Practitioner's Docket No. SPC520USCNT1 *PATENT*

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patent No.: 6,248,775 Issued: June 19, 2001
Expiration Date: August 25, 2012

Inventors: Vazquez; Michael L.; Mueller; Richard A.; Talley; John J.; Getman; Daniel P.; DeCrescenzo; Gary A.; Freskos; John N.; Bertenshaw; Deborah E.; Heintz; Robert M.

Title: α- and β-Amino Acid Hydroxyethylamino Sulfonamides Useful as Retroviral Protease Inhibitors

Mail Stop Patent Extension
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

APPLICATION FOR EXTENSION OF PATENT TERM (37 C.F.R. § 1.740)

Pursuant to 35 U.S.C. §156(d) and 37 C.F.R. §1.740, G. D. Searle LLC ("Applicant") as Assignee and patent owner of the above-captioned patent, hereby petitions for extension of U.S. Patent No. 6,248,775 (the '775 Patent). In support of such Petition, Applicant provides the following information:

I. SIGNATURE REQUIREMENTS (37 C.F.R. §1.730)

A. IDENTIFICATION OF PERSON(S) SUBMITTING THE APPLICATION

I, Alana G. Kriegsman, represent that I am a registered practitioner appointed by the patent owner of record.

B. RECORDAL OF ASSIGNMENT IN PTO

This application is a Continuation of U.S.S.N. 08/294,468, filed 08-23-1994, issued 10/19/1999 as U.S. Patent No. 5,968,942. An assignment of U.S.S.N. 08/294,468 was recorded: Date: 10/31/1994 at Reel/Frame: 007254/0618 from the named inventors to G.D. Searle & Co., and an assignment of U.S.S.N. 08/294,468 was recorded: Date: 07/13/2006 at Reel/Frame: 017921/0735 from G.D. Searle & Co. to G.D. Searle LLC.

C. PROOF OF AUTHORIZATION OF SIGNATORY TO ACT ON BEHALF OF THE PATENT OWNER

Attached as **Exhibit 1** is a Power of Attorney establishing authorization of Alana G. Kriegsman to act on behalf of the patent owner.

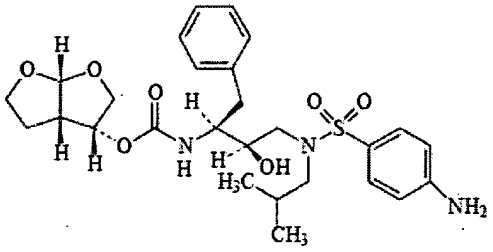
II. APPLICATION REQUIREMENTS (37 C.F.R. §1.740)

A. IDENTIFICATION OF APPROVED PRODUCT (1.740(a)(1))

The United States Food and Drug Administration ("FDA") has approved New Drug Application ("NDA") No. 21-976 for PREZISTA™ (darunavir). The active ingredient of PREZISTA is darunavir which is contained in the drug product as darunavir ethanolate. A copy of the approved labeling is attached hereto as **Exhibit 2**.

The chemical name for darunavir is [(1*S*,2*R*)-3-[[(4-aminophenyl)sulfonyl](2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-carbamic acid (3*R*,3a*S*,6a*R*)-hexahydrofuro[2,3-*b*]furan-3-yl ester and the molecular formula is $C_{27}H_{37}N_3O_7S$.

Darunavir has the following structural formula:



Each tablet of PREZISTA contains darunavir ethanolate equivalent to 300 mg of darunavir.

B. IDENTIFICATION OF THE FEDERAL STATUTE UNDER WHICH REGULATORY REVIEW OCCURRED (1.740(a)(2))

Regulatory review for this product occurred under the Federal Food Drug & Cosmetic Act ("FDC Act") §505(b), 21 U.S.C. §355 (new drugs).

C. DATE OF APPROVAL (1.740(a)(3))

The FDA approved No. 21-976 for PREZISTA™ for commercial marketing or use under §505 of the FDC Act on June 23, 2006.

D. IDENTIFICATION OF ACTIVE INGREDIENTS AND PREVIOUS APPROVAL INFORMATION (1.740(a)(4))

PREZISTA™ (darunavir) is a human drug product, the sole active ingredient of which is darunavir. Neither darunavir, nor any salt or ester thereof, has been previously approved, alone or in combination, for commercial marketing or use under the Food, Drug & Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act.

E. TIMELY SUBMISSION OF APPLICATION (60 DAYS) (1.740(a)(5)

This application is being submitted within the sixty-day time period permitted for submission pursuant to 37 C.F.R. §1.720(f). The last date this application may be submitted is August 22, 2006.

F. IDENTIFICATION OF PATENT (1.740(a)(6), (7), (8))

Name of the Inventors:	Michael L. Vazquez Richard A. Mueller John J. Talley Daniel P. Getman Gary A. DeCrescenzo John N. Freskos Deborah E. Bertenshaw Robert M. Heintz
Patent No.	6,248,775
Date of Issue:	June 19, 2001
Date of Original Expiration:	August 25, 2012

A copy of the patent, including the entire specification (with claims) and drawings is attached as **Exhibit 3**.

A copy of the U.S. Patent & Trademark Office Maintenance Fee Statement is attached as **Exhibit 4**.

A terminal disclaimer pursuant to 37 C.F.R. § 1.321(a) was filed in the '775 Patent disclaiming the terminal part of the statutory tem of any patented which would extend beyond the expiration date of the full statutory term defined in 35 U.S.C. §§ 154-156 and 173 of U.S. Patents 5,843,946; 5,968,942; 6,046,190 and 6,060,476. A copy of the disclaimer is attached as **Exhibit 5**. The '775 Patent remains commonly owned with U.S. Patents 5,843,946; 5,968,942; 6,046,190 and 6,060,476.

No certificate of correction or reexamination certificate has issued in the '775 Patent.

G. IDENTIFICATION OF CLAIMS READING ON THE APPROVED PRODUCT (1.740(a)(9))

The '775 Patent claims the active ingredient of the approved Product which is darunavir (and also claims darunavir ethanolate). The '775 Patent includes 18 claims, of which claims 3 and 7 claim darunavir (and darunavir ethanolate). A claim chart that lists each applicable claim of the '775 Patent and demonstrates the manner in which each claim reads on the approved Product is attached as **Exhibit 6**.

H. RELEVANT DATES AND INFORMATION (1.740(a)(10))

The '775 Patent claims a human drug.

The effective date of the investigational new drug (IND) application was January 20, 2003 and the IND No. is 62,477.

The new drug application (NDA) was initially submitted on December 22, 2005 and was received by the FDA on December 23, 2005. The NDA No. is 21-976.

The NDA was approved on June 23, 2006.

I. DESCRIPTION OF SIGNIFICANT ACTIVITIES OF APPLICANT DURING REGULATORY REVIEW (1.740(a)(11))

Attached as **Exhibit 7** is a "DESCRIPTION OF SIGNIFICANT ACTIVITIES OF APPLICANT DURING REGULATORY REVIEW" that provides a description of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved Product and the significant dates applicable to such activities.

J. STATEMENT THAT APPLICANT IS ELIGIBLE FOR EXTENSION (1.740(a)(12))

Attached as **Exhibit 8** is a "STATEMENT THAT APPLICANT IS ELIGIBLE FOR EXTENSION AND LENGTH OF EXTENSION CLAIMED" that states that in the opinion of the applicant the '775 Patent is eligible for the extension and the length of extension claimed, including how the length of extension was determined.

K. ACKNOWLEDGEMENT OF DUTY OF DISCLOSURE (1.740(a)(13))

I, Alana G Kriegsman, the person signing below, acknowledge the duty to disclose to the Director of the U.S. Patent and Trademark Office and to the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension which is being sought herein.

L. FEE (1.740(a)(14))

The Application fee due is $1,120.00 (37 C.F.R. § 1.740(a)(15) and § 1.20(j).

Authorization is hereby made to charge the amount of $1,120.00 to Deposit Account No. 10-0750/SPC520/AKG.

Please also charge any additional fees required by this paper or credit any overpayment to Deposit Account No. 10-0750/SPC520/AKG.

M. CORRESPONDENCE

Please direct all inquiries and correspondence relating to this application to:

Phillip Johnson, Esq.
Johnson & Johnson
One Johnson Drive
New Brunswick, NJ 08816

Attn: Alana Kriegsman

Phone: (732) 524-1495
Facsimile: (732) 524-2808

N. COPIES (§ MPEP 2753 (8th Edition, Rev. No. 4))

Four additional copies of this application are attached, making a total of five copies being submitted.

Conclusion

In conclusion, on the basis of the information provided herein, Applicant respectfully asserts that U.S. Patent No. 6,248,775 is entitled to the requested 717 day extension of its term to August 12, 2014.

Prompt action on this application is respectfully requested.

Date: 15 August 2006

Alana Kriegsman

Signature of Practitioner

Reg. No.: 41,744
Tel. No.: 732-524-1495
Customer No.: 000027777

Alana G. Kriegsman, Esq.
Johnson & Johnson
One Johnson Drive
New Brunswick, NJ 08816
U.S.A.

Exhibit 1 **Power of Attorney**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patent No.: 6,248,775 Issued: June 19, 2001
Expiration Date: August 25, 2012

Inventors: Vazquez; Michael L.; Mueller; Richard A.; Talley; John J.; Getman; Daniel P.; DeCrescenzo; Gary A.; Freskos; John N.; Bertenshaw; Deborah E.; Heintz; Robert M.

Title: α- and ß-Amino Acid Hydroxyethylamino Sulfonamides Useful as Retroviral Protease Inhibitors

Limited Power of Attorney

The undersigned, who is empowered to sign this certificate on behalf of the assignee, hereby appoints the following practitioners for the limited purpose of filing and prosecuting an extension of U.S. Patent No. 6,248,775 pursuant to 35 U.S.C. §156(d) and 37 C.F.R. §1.740:

Phillip Johnson, Esq. (Registration Number: 27,200)
Steven P. Berman, Esq. (Registration Number: 24,772)
Bernard F. Plantz, Esq. (Registration Number: 32,091)
Myra H. McCormack, Esq. (Registration Number: 36,602)
Mary A. Appollina, Esq. (Registration Number: 34,087)
Alana G. Kriegsman, Esq. (Registration Number: 41,747)

Johnson & Johnson
One Johnson Drive
New Brunswick, NJ 08816
Phone: (732) 524-1495
Facsimile: (732) 524-2808

Certification Under 37 C.F.R §3.73(b)

G. D. Searle LLC., a Limited Liability Corporation, certifies that it is the assignee of the entire right, title and interest in the patent application identified above by virtue of either:

☒ A chain of title from the inventor(s), or the patent application identified above, to the current assignee as shown below:

From: Inventors: Vazquez; Michael L.; Mueller; Richard A.; Talley; John J.; Getman; Daniel P.; DeCrescenzo; Gary A.; Freskos; John N.; Bertenshaw; Deborah E.; Heintz; Robert M.
To: G.D. Searle & Co.
The document was recorded in the Patent and Trademark Office at Reel 007254, Frame 0618, or for which a copy thereof is attached.

From: G.D. Searle & Co.
To: G.D. Searle LLC

The document was recorded in the Patent and Trademark Office at Reel 017921, Frame 0735, or for which a copy thereof is attached.

From:
To:
The document was recorded in the Patent and Trademark Office at Reel , Frame , or for which a copy thereof is attached.

☒ Copies of assignments or other documents in the chain of title are attached.

The undersigned has reviewed all the documents in the chain of title of the patent application identified above and, to the best of undersigned's knowledge and belief, title is in the assignee identified above.

The undersigned (whose title is supplied below) is empowered to sign this certificate on behalf of the assignee.

I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful false statements, and the like so made, are punishable by fine or imprisonment, or both, under Section 1001, Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

3 August 2006
Date

Signature

Grover F. Fuller, Jr.
Typed or Printed Name

Attorney-in-Fact
Title

G. D. Searle LLC
Company

Case No. 2705/3

ASSIGNMENT (JOINT, SEPARATE)

For Ten Dollars and other valuable considerations, the receipt and sufficiency of which are hereby acknowledged, I,

Michael L. Vazquez: 233 Saratoga Court, Gurnee, IL 60031;

Richard A. Mueller: 562 Stonegate Terrace, Glencoe, IL 60022;

hereby sell, assign, transfer and convey unto G.D. SEARLE & CO., a Delaware corporation, whose address is Post Office Box 5110, Chicago, Illinois, 60680, its successors and assigns, the entire right, title and interest in and to our invention in α- AND β-AMINO ACID HYDROXYETHYLAMINO SULFONAMIDES USEFUL AS RETROVIRAL PROTEASE INHIBITORS described in an application for United States Letters Patent therefore, executed on even date herewith, and in and to all Letters Patent of the United States and foreign countries, in which I am a joint inventor with John J. Talley, Daniel P. Getman, Gary A. DeCrescenzo, John N. Freskos, Deborah E. Bertenshaw, and Robert M. Heintz including any divisions, continuations, reissues and extensions thereof that may be obtained therefore; and I agree that I will, without additional compensation, but without cost to me, promptly communicate to said G.D. SEARLE & CO., or its representatives any facts known to me respecting said invention whenever requested, and testify in any legal proceedings, sign all lawful papers, and execute all divisional, continuing and reissue applications, make all rightful oaths and generally do everything possible to aid our said assignee, its successors and assigns, as and when requested by them, in obtaining and enforcing proper patent protection for said invention or inventions and improvements in the United States and all countries foreign thereto; and I hereby authorize and request the Commissioner of Patents to issue any and all Letters Patent that may be granted for said invention to said G.D. SEARLE & CO., its successors and assigns.

Signed and sealed this 26 day of OCTOBER, 1994.

Michael L. Vazquez 10/26/94
Michael L. Vazquez

Richard A. Mueller 10/24/94
Richard A. Mueller

State of ILLINOIS)
)S.S
County of COOK)

On the day and year aforesaid, appeared Michael L. Vazquez and Richard A. Mueller, personally known to me, and by me personally known to be the persons who executed the above instrument, who, being duly sworn, acknowledged that they executed the above instrument as their free and voluntary act.

Deborah E. Ryan 10/26/94
Notary Public

OFFICIAL SEAL
DEBORAH E RYAN
NOTARY PUBLIC, STATE OF ILLINOIS
MY COMMISSION EXPIRES:06/13/98

Case No. 2705/3

ASSIGNMENT (JOINT, SEPARATE)

For Ten Dollars and other valuable considerations, the receipt and sufficiency of which are hereby acknowledged, I,

Deborah E. Bertenshaw: 8758 Pine Ave., Brentwood, MO 63144

hereby sell, assign, transfer and convey unto G.D. SEARLE & CO., a Delaware corporation, whose address is Post Office Box 5110, Chicago, Illinois, 60680, its successors and assigns, the entire right, title and interest in and to our invention in α- AND β-AMINO ACID HYDROXYETHYLAMINO SULFONAMIDES USEFUL AS RETROVIRAL PROTEASE INHIBITORS described in an application for United States Letters Patent therefore, executed on even date herewith, and in and to all Letters Patent of the United States and foreign countries, in which I am a joint inventor with Michael L. Vazquez, Richard A. Mueller, John J. Talley, Daniel P. Getman, Gary A. DeCrescenzo, John N. Freskos, and Robert M. Heintz including any divisions, continuations, reissues and extensions thereof that may be obtained therefore; and I agree that I will, without additional compensation, but without cost to me, promptly communicate to said G.D. SEARLE & CO., or its representatives any facts known to me respecting said invention whenever requested, and testify in any legal proceedings, sign all lawful papers, and execute all divisional, continuing and reissue applications, make all rightful oaths and generally do everything possible to aid our said assignee, its successors and assigns, as and when requested by them, in obtaining and enforcing proper patent protection for said invention or inventions and improvements in the United States and all countries foreign thereto; and I hereby authorize and request the Commissioner of Patents to issue any and all Letters Patent that may be granted for said invention to said G.D. SEARLE & CO., its successors and assigns.

Signed and sealed this 20 day of October, 1994.

Deborah E. Bertenshaw

Deborah E. Bertenshaw

State of Missouri)
)S.S
County of St Louis)

On the day and year aforesaid, appeared Deborah E. Bertenshaw, personally known to me, and by me personally known to be the persons who executed the above instrument, who, being duly sworn, acknowledged that they executed the above instrument as their free and voluntary act.

Karol J Wilder

Notary Public

KAROL J WILDER
NOTARY PUBLIC STATE OF MISSOURI
ST. LOUIS COUNTY
MY COMMISSION EXP. SEPT 25,1998

Case No. 2705/3

ASSIGNMENT (JOINT, SEPARATE)

For Ten Dollars and other valuable considerations, the receipt and sufficiency of which are hereby acknowledged, I,

John J. Talley:	8772 Pine Ave., Brentwood, MO 63144
Daniel P. Getman:	66 Sunny Hill Court, Chesterfield, MO 63017
Gary A. DeCrescenzo:	536 Schrader Farm Dr., St. Peters, MO 63376
John N. Freskos:	7572 York, Clayton, MO 63105
Robert M. Heintz:	603 Nancy Place, Ballwin, MO 63021

hereby sell, assign, transfer and convey unto G.D. SEARLE & CO., a Delaware corporation, whose address is Post Office Box 5110, Chicago, Illinois, 60680, its successors and assigns, the entire right, title and interest in and to our invention in α- AND β-AMINO ACID HYDROXYETHYLAMINO SULFONAMIDES USEFUL AS RETROVIRAL PROTEASE INHIBITORS described in an application for United States Letters Patent therefore, executed on even date herewith, and in and to all Letters Patent of the United States and foreign countries, in which I am a joint inventor with Michael L. Vazquez, Richard A. Mueller and Deborah E. Bertenshaw including any divisions, continuations, reissues and extensions thereof that may be obtained therefore; and I agree that I will, without additional compensation, but without cost to me, promptly communicate to said G.D. SEARLE & CO., or its representatives any facts known to me respecting said invention whenever requested, and testify in any legal proceedings, sign all lawful papers, and execute all divisional, continuing and reissue applications, make all rightful oaths and generally do everything possible to aid our said assignee, its successors and assigns, as and when requested by them, in obtaining and enforcing proper patent protection for said invention or inventions and improvements in the United States and all countries foreign thereto; and I hereby authorize and request the Commissioner of Patents to issue any and all Letters Patent that may be granted for said invention to said G.D. SEARLE & CO., its successors and assigns.

Signed and sealed this 27th day of October, 1994.

John J. Talley
John J. Talley

Daniel P. Getman
Daniel P. Getman

Gary A. DeCrescenzo
Gary A. DeCrescenzo

John N. Freskos
John N. Freskos

Robert M. Heintz
Robert M. Heintz

State of Missouri)
)S.S
County of St. Charles)

On the day and year aforesaid, appeared John J. Talley, Daniel P. Getman, Gary A. DeCrescenzo, John N. Freskos, Robert M. Heintz, personally known to me, and by me personally known to be the persons who executed the above instrument, who, being duly sworn, acknowledged that they executed the above instrument as their free and voluntary act.

Brenda K. Lammers
Notary Public

BRENDA K. LAMMERS
Notary Public-Notary Seal
STATE OF MISSOURI
ST CHARLES COUNTY
My Appointment Expires FEB 15, 1997

UNITED STATES PATENT AND TRADEMARK OFFICE

UNDER SECRETARY OF COMMERCE FOR INTELLECTUAL PROPERTY AND
DIRECTOR OF THE UNITED STATES PATENT AND TRADEMARK OFFICE

JULY 13, 2006

PTAS

500125415A

500125415A

JOSEPH M. SKERPON
1001 G STREET N.W.
WASHINGTON, DC 20001

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE ASSIGNMENT SEARCH ROOM ON THE REEL AND FRAME NUMBER REFERENCED BELOW.

PLEASE REVIEW ALL INFORMATION CONTAINED ON THIS NOTICE. THE INFORMATION CONTAINED ON THIS RECORDATION NOTICE REFLECTS THE DATA PRESENT IN THE PATENT AND TRADEMARK ASSIGNMENT SYSTEM. IF YOU SHOULD FIND ANY ERRORS OR HAVE QUESTIONS CONCERNING THIS NOTICE, YOU MAY CONTACT THE EMPLOYEE WHOSE NAME APPEARS ON THIS NOTICE AT 571-272-3350. PLEASE SEND REQUEST FOR CORRECTION TO: U.S. PATENT AND TRADEMARK OFFICE, MAIL STOP: ASSIGNMENT SERVICES BRANCH, P.O. BOX 1450, ALEXANDRIA, VA 22313.

RECORDATION DATE: 07/13/2006

REEL/FRAME: 017921/0735
NUMBER OF PAGES: 3

BRIEF: CHANGE OF NAME (SEE DOCUMENT FOR DETAILS).
DOCKET NUMBER: 101765.80234

ASSIGNOR:
G.D. SEARLE & CO.

DOC DATE: 12/28/2000

ASSIGNEE:
G.D. SEARLE LLC
1209 ORANGE STREET
C/O THE CORPORATION TRUST COMPANY,
CORPORATION TRUST CENTER
WILMINGTON, DELAWARE 19801

SERIAL NUMBER: 08294468
PATENT NUMBER: 5968942

FILING DATE: 08/23/1994
ISSUE DATE: 10/19/1999

TITLE: ALPHA- AND BETA-AMINO ACID HYDROXYETHYLAMINO SULFONAMIDES USEFUL AS RETROVIRAL PROTEASE INHIBITORS

ALLYSON PURNELL, EXAMINER
ASSIGNMENT SERVICES BRANCH
PUBLIC RECORDS DIVISION

Exhibit 2

Approved Labeling for PREZISTA™

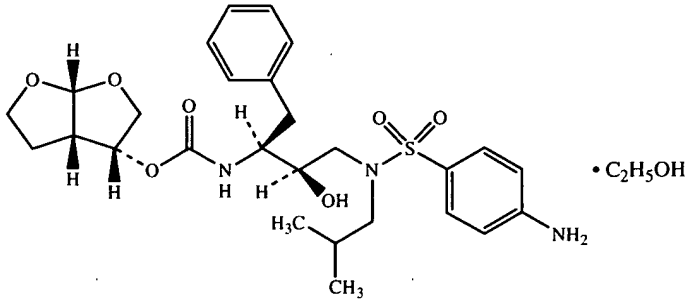
PREZISTA™* (Tibotec, Inc.)
(darunavir)

Tablets

DESCRIPTION

PREZISTA™ (darunavir) is an inhibitor of the human immunodeficiency virus (HIV) protease.

PREZISTA™ (darunavir), in the form of darunavir ethanolate, has the following chemical name: [(1*S*,2*R*)-3-[[(4-aminophenyl)sulfonyl](2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-carbamic acid (3*R*,3a*S*,6a*R*)-hexahydrofuro[2,3-*b*]furan-3-yl ester monoethanolate. Its molecular formula is $C_{27}H_{37}N_3O_7S \cdot C_2H_5OH$ and its molecular weight is 593.73. Darunavir ethanolate has the following structural formula:



Darunavir ethanolate is a white to off-white powder with a solubility of approximately 0.15 mg/mL in water at 20°C.

PREZISTA is available as an orange, oval-shaped, film-coated tablet for oral administration. Each tablet contains darunavir ethanolate equivalent to 300 mg of darunavir. Each tablet also contains the inactive ingredients colloidal silicon dioxide, crospovidone, magnesium stearate, and microcrystalline cellulose. The tablet film coating, OPADRY® Orange, contains FD&C Yellow No. 6, polyethylene glycol 3350, polyvinyl alcohol-partially hydrolyzed, talc, and titanium dioxide.

All dosages for PREZISTA are expressed in terms of the free form of darunavir.

MICROBIOLOGY

Mechanism of Action

Darunavir is an inhibitor of the HIV-1 protease. It selectively inhibits the cleavage of HIV encoded Gag-Pol polyproteins in infected cells, thereby preventing the formation of mature virus particles.

Antiviral Activity

*Trademark of Tibotec, Inc.

Darunavir exhibits activity against laboratory strains and clinical isolates of HIV-1 and laboratory strains of HIV-2 in acutely infected T-cell lines, human peripheral blood mononuclear cells and human monocytes/macrophages with median EC_{50} values ranging from 1.2 to 8.5 nM (0.7 to 5.0 ng/mL). Darunavir demonstrates antiviral activity in cell culture against a broad panel of HIV-1 group M (A, B, C, D, E, F, G), and group O primary isolates with EC_{50} values ranging from < 0.1 to 4.3 nM. The EC_{50} value of darunavir increases by a median factor of 5.4 in the presence of human serum. Darunavir did not show antagonism when studied in combination with the protease inhibitors amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, or tipranavir, the N(t)RTIs abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, zalcitabine, or zidovudine, the NNRTIs delavirdine, efavirenz, or nevirapine, and the fusion inhibitor enfuvirtide.

Resistance

Cell Culture: HIV-1 isolates with a decreased susceptibility to darunavir have been selected in cell culture and obtained from subjects treated with darunavir/ritonavir. Darunavir-resistant virus derived in cell culture from wild-type HIV had 6- to 21-fold decreased susceptibility to darunavir and harbored 3 to 6 of the following amino acid substitutions S37N/D, R41E/S/T, K55Q, K70E, A71T, T74S, V77I, or I85V in the protease. Selection in cell culture of darunavir resistant HIV-1 from nine HIV-1 strains harboring multiple protease inhibitor resistance-associated mutations resulted in the overall emergence of 22 mutations in the protease gene, including L10F, V11I, I13V, I15V, G16E, L23I, V32I, L33F, S37N, M46I, I47V, I50V, F53L, L63P, A71V, G73S, L76V, V82I, I84V, T91A/S, and Q92R, of which L10F, V32I, L33F, S37N, M46I, I47V, I50V, L63P, A71V, and I84V were the most prevalent. These darunavir-resistant viruses had at least eight protease mutations and exhibited 50- to 641-fold decreases in darunavir susceptibility with final EC_{50} values ranging from 125 nM to 3461 nM.

Clinical studies of darunavir/ritonavir in treatment-experienced subjects

In the Phase 2b Studies TMC114-C213 and TMC114-C202 and the TMC114-C215/C208 analysis, multiple protease inhibitor-resistant HIV-1 isolates from highly treatment-experienced subjects who received PREZISTA/rtv 600/100 mg b.i.d. and experienced virologic failure, either by rebound, or by never being suppressed, developed amino acid substitutions that were associated with a decrease in susceptibility to darunavir. The amino acid substitution V32I developed on PREZISTA/rtv 600/100 mg b.i.d. in greater than 30% of virologic failure isolates and substitutions at amino acid position I54 developed in greater than 20% of virologic failure isolates. Other substitutions that developed in 10% to 20% of PREZISTA/rtv virologic failure isolates occurred at amino acid positions I15, L33, I47, G73 and L89. The median darunavir phenotype (fold change from reference) of the virologic failure isolates was 21-fold at baseline and 94-fold at failure. Amino acid substitutions were also observed in the protease cleavage sites of some darunavir virologic failure isolates. The resistance profile in treatment-naïve subjects has not been characterized.

Cross-resistance

Cross-resistance among protease inhibitors has been observed. Darunavir has a < 10-fold decreased susceptibility in cell culture against 90% of 3309 clinical isolates resistant to amprenavir, atazanavir,

indinavir, lopinavir, nelfinavir, ritonavir, saquinavir and/or tipranavir showing that viruses resistant to these protease inhibitors remain susceptible to darunavir. In Studies TMC114-C213 and TMC114-C202 and the TMC114-C215/C208 analysis, 60% (88/147) of subjects on darunavir/rtv whose baseline isolates had decreased susceptibility to tipranavir (tipranavir fold change > 3) demonstrated a decrease of ≥ 1 $\log_{10}$ in viral load at week 24, and 36% (53/147) achieved < 50 copies/mL plasma HIV RNA levels.

Darunavir-resistant viruses were not susceptible to amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir or saquinavir in cell culture. However, six of nine darunavir-resistant viruses selected in cell culture from protease inhibitor-resistant viruses showed a fold change in EC_{50} values < 3 for tipranavir, indicative of limited cross-resistance between darunavir and tipranavir. Of the viruses isolated from subjects experiencing virologic failure on darunavir/ritonavir 600/100 mg b.i.d., greater than 50% were still susceptible to tipranavir while less than 5% were susceptible to other protease inhibitors (amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, or saquinavir).

Cross-resistance between darunavir and the nucleoside/nucleotide reverse transcriptase inhibitors, the non-nucleoside reverse transcriptase inhibitors or the fusion inhibitor is unlikely because the viral targets are different.

Baseline Genotype/Phenotype and Virologic Outcome Analyses

Genotypic and/or phenotypic analysis of baseline virus may aid in determining darunavir susceptibility before initiation of PREZISTA/rtv 600/100 mg b.i.d. therapy. Analyses were conducted to evaluate the impact of specific baseline protease inhibitor resistance-associated mutations and the number of protease inhibitor resistance-associated mutations at baseline on virologic response. Both specific mutations and the number of baseline mutations, as well as susceptible drugs in the optimized background regimen and enfuvirtide use, affected PREZISTA/rtv response rates in Phase 2b Studies TMC114-C213 and TMC114-C202.

The presence at baseline of the mutations V32I, I47V, or I54L or M, was associated with a decreased virologic response to darunavir and decreased susceptibility to darunavir. In addition, a diminished virologic response was observed in subjects with ≥ 7 protease inhibitor resistance-associated mutations (any change at amino acid positions 30, 32, 36, 46, 47, 48, 50, 53, 54, 73, 82, 84, 88, or 90) at baseline (see Table 1). In a supportive analysis of Studies TMC114-C213 and TMC114-C202 and the TMC114-C215/C208 analysis, the presence at baseline of three or more of the mutations V11I, V32I, L33F, I47V, I50V, I54L or M, G73S, L76V, I84V or L89V was associated with a decreased virologic response to PREZISTA/rtv (the proportion of subjects achieving viral load < 50 plasma HIV RNA copies/mL at week 24 was 50%, 22% and 10% when the baseline genotype had 0-2, 3 and ≥ 4 of these mutations, respectively). Conclusions regarding the relevance of particular mutations or mutational patterns are subject to change pending additional data.

Table 1: Response to PREZISTA/rtv 600/100 mg b.i.d. by Baseline Number of Protease Inhibitor Resistance-Associated Mutations: As-Treated Analysis of Studies TMC114-C213 and TMC114-C202

	Prezista/rtv 600/100 mg (n = 125)				Comparative Arm (n = 120)			
PI Mutations^	**n**	**Proportion of subjects with ≥ 1 log_{10} decrease at Week 24**	**Proportion of subjects with < 50 copies/ mL at Week 24**	**Median $DAVG_{24}$**	**n**	**Proportion of subjects with ≥ 1 log_{10} decrease at Week 24**	**Proportion of subjects with < 50 copies/ mL at Week 24**	**Median $DAVG_{24}$**
0 - 4	57	81%	46%	-2.16	52	23%	13%	-0.57
5 - 6	54	67%	52%	-2.13	51	24%	16%	-0.43
≥7	14	21%	14%	-0.87	17	6%	0%	-0.13
^ Any change at protease amino acid positions 30, 32, 36, 46, 47, 48, 50, 53, 54, 73, 82, 84, 88 and 90								

Baseline darunavir phenotype (shift in susceptibility relative to reference) was shown to be a predictive factor of virologic outcome. Response rates assessed by baseline darunavir phenotype are shown in Table 2. These baseline phenotype groups are based on the select subject populations in the Studies TMC114-C213 and TMC114-C202 and the TMC114-C215/C208 analysis, and are not meant to represent definitive clinical susceptibility breakpoints for PREZISTA/rtv. The data are provided to give clinicians information on the likelihood of virologic success based on pre-treatment susceptibility to darunavir in protease inhibitor-experienced patients.

Table 2: Response to PREZISTA/rtv 600/100 mg b.i.d. by Baseline Darunavir Phenotype: As-Treated Analysis of Studies TMC114-C213, TMC114-C202, and TMC114-C215/C208

Baseline Darunavir Phenotype N = 340 (fold change ranges)	Proportion of subjects with ≥1 log_{10} decrease at Week 24	Proportion of subjects with < 50 copies/mL at Week 24	Clinical Response Range
All ranges	70% 238/340	43% 147/340	Overall Response
0 - 2	88% 119/136	60% 82/136	Higher than Overall Response
> 2 - 7	73% 62/85	47% 40/85	Similar to Overall Response
> 7 - 30	52% 33/63	24% 15/63	Lower than Overall Response
> 30	43% 24/56	18% 10/56	Lower than Overall Response

CLINICAL PHARMACOLOGY

Pharmacokinetics in Adults

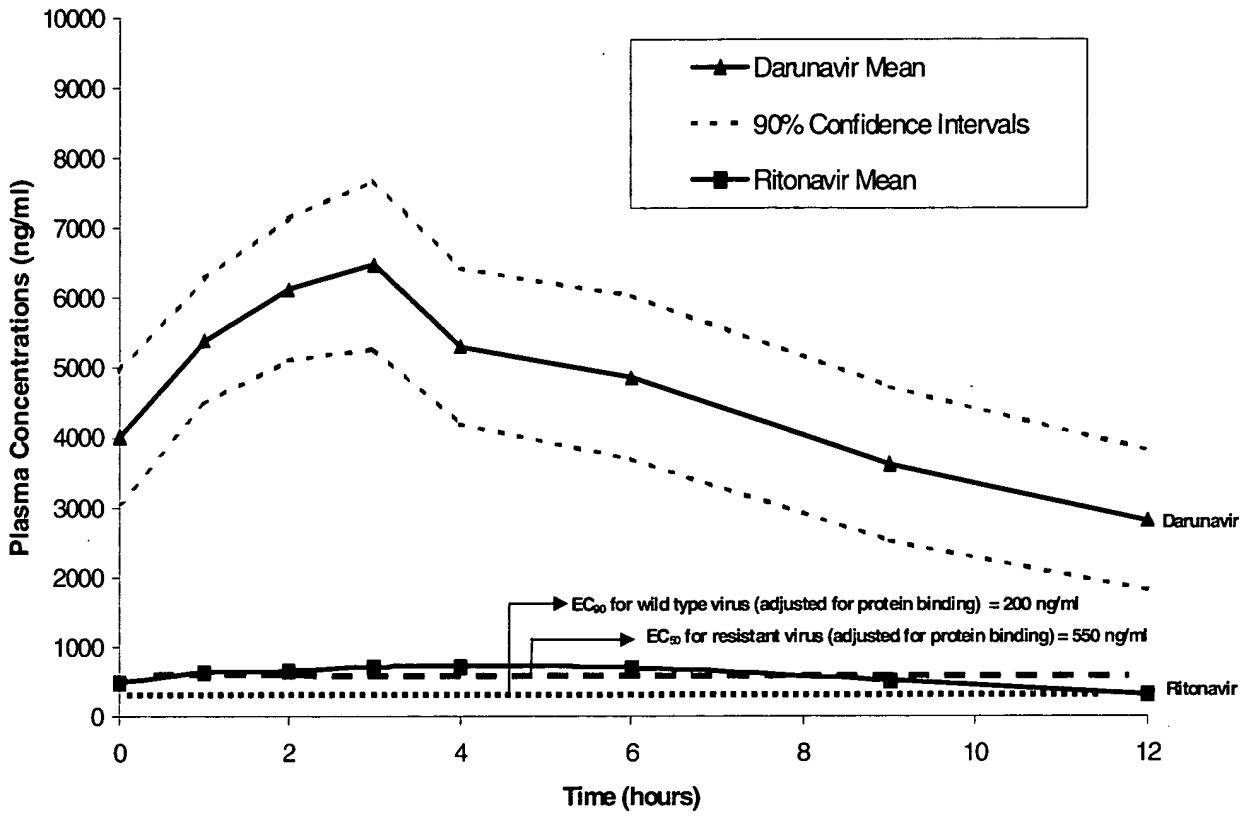
The pharmacokinetics of darunavir, co-administered with low dose ritonavir (100 mg twice daily), have been evaluated in healthy adult volunteers and in HIV-1 infected subjects. Table 3 displays the population pharmacokinetic estimates of darunavir from an analysis of integrated data from Studies TMC114-C213 and TMC114-C202 of 119 subjects administered the darunavir/ritonavir 600/100 mg b.i.d. dose. Darunavir is primarily metabolized by CYP3A. Ritonavir inhibits CYP3A, thereby increasing the plasma concentrations of darunavir. When a single dose of 600 mg darunavir was given orally in combination with 100 mg ritonavir b.i.d., there was an approximate 14-fold increase in the systemic exposure of darunavir. Therefore, PREZISTA should only be used in combination with 100 mg of ritonavir to achieve sufficient exposures of darunavir.

Table 3: Population Pharmacokinetic Estimates of Darunavir at the Darunavir/Ritonavir 600/100 mg b.i.d. dose (Integrated data from TMC114-C213 and TMC114-C202, Primary 24-Week Analysis)

Parameter	**Darunavir/Ritonavir 600/100 mg b.i.d. N = 119**
AUC_{12h} (ng·h/mL)	
Geometric Mean ± Standard Deviation	62349 ± 16143
Median (Range)	61668 (33857-106490)
C_{0h} (ng/mL)	
Geometric Mean ± Standard Deviation	3578 ± 1151
Median (Range)	3539 (1255-7368)
N = number of subjects with data.	

Figure 1 displays the mean plasma concentrations of darunavir and ritonavir at steady-state for the darunavir/ritonavir 600/100 mg b.i.d. dose.

Figure 1: Mean Steady-State Plasma Concentration-Time Profiles of Darunavir and Ritonavir at 600/100 mg b.i.d. at Week 4 (Integrated data from TMC114-C213 and TMC114-C202, Primary 24-Week Analysis)



Absorption and Bioavailability: Darunavir, co-administered with 100 mg ritonavir twice daily, was absorbed following oral administration with a T_{max} of approximately 2.5-4 hours. The absolute oral bioavailability of a single 600 mg dose of darunavir alone and after co-administration with 100 mg ritonavir twice daily was 37% and 82%, respectively.

Effects of Food on Oral Absorption: When administered with food, the C_{max} and AUC of darunavir, co-administered with ritonavir, is approximately 30% higher relative to the fasting state. Therefore, PREZISTA tablets, co-administered with ritonavir, should always be taken with food. Within the range of meals studied, darunavir exposure is similar. The total caloric content of the various meals evaluated ranged from 240 Kcal (12 gms fat) to 928 Kcal (56 gms fat).

Distribution: Darunavir is approximately 95% bound to plasma proteins. Darunavir binds primarily to plasma alpha 1-acid glycoprotein (AAG).

Metabolism: *In vitro* experiments with human liver microsomes (HLMs) indicate that darunavir primarily undergoes oxidative metabolism. Darunavir is extensively metabolized by CYP enzymes, primarily by CYP3A. A mass balance study in healthy volunteers showed that after a single dose administration of 400 mg ^{14}C-darunavir, co-administered with 100 mg ritonavir, the majority of the radioactivity in the plasma was due to darunavir. At least 3 oxidative metabolites of darunavir have been identified in humans; all showed activity that was at least 90% less than the activity of darunavir against wild-type HIV.

Elimination: A mass balance study in healthy volunteers showed that after single dose administration of 400 mg ^{14}C-darunavir, co-administered with 100 mg ritonavir, approximately 79.5% and 13.9% of the administered dose of ^{14}C-darunavir was recovered in the feces and urine, respectively. Unchanged darunavir accounted for approximately 41.2% and 7.7% of the administered dose in feces and urine, respectively. The terminal elimination half-life of darunavir was approximately 15 hours when combined with ritonavir. After intravenous administration, the clearance of darunavir, administered alone and co-administered with 100 mg twice daily ritonavir, was 32.8 L/h and 5.9 L/h, respectively.

Special Populations

Hepatic Impairment: Darunavir primarily undergoes hepatic metabolism. PREZISTA has not been studied in patients with varying degrees of hepatic impairment (see PRECAUTIONS, *Patients with co-existing conditions*, *Hepatic Impairment* and DOSAGE AND ADMINISTRATION).

Hepatitis B or Hepatitis C Virus Co-infection: The primary 24-week analysis of the data from Study TMC114-C213 in 31 HIV-1 infected subjects indicated that hepatitis B and/or hepatitis C virus co-infection status had no apparent effect on the exposure of darunavir.

Renal Impairment: Results from a mass balance study with ^{14}C-darunavir/ritonavir showed that approximately 7.7% of the administered dose of darunavir is excreted in the urine as unchanged drug. As darunavir and ritonavir are highly bound to plasma proteins, it is unlikely that they will be significantly removed by hemodialysis or peritoneal dialysis. Population pharmacokinetic analysis showed that the pharmacokinetics of darunavir were not significantly affected in HIV infected subjects with moderate renal impairment (CrCL between 30-60 mL/min, n=20). There are no pharmacokinetic data available in HIV-1 infected patients with severe renal impairment or end stage renal disease. (see PRECAUTIONS, *Patients with co-existing conditions*, *Renal Impairment*, and DOSAGE AND ADMINISTRATION).

Gender: Population pharmacokinetic analysis showed higher mean darunavir exposure (16.8%) in HIV infected females (n=68) compared to males. This difference is not clinically relevant.

Race: Population pharmacokinetic analysis of darunavir in HIV infected subjects indicated that race had no apparent effect on the exposure to darunavir.

Geriatric Patients: Population pharmacokinetic analysis in HIV infected subjects showed that darunavir pharmacokinetics are not considerably different in the age range (18 to 75 years) evaluated in HIV infected subjects (n=12, age $\geq$ 65) (see PRECAUTIONS, *Geriatric Use*).

Pediatric Patients: The pharmacokinetics of darunavir in combination with ritonavir in pediatric patients has not been established. There are insufficient data at this time to recommend a dose.

Drug Interactions: See also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS, Drug Interactions.

Darunavir and ritonavir are both inhibitors of CYP3A. Co-administration of darunavir and ritonavir with drugs primarily metabolized by CYP3A may result in increased plasma concentrations of such

drugs, which could increase or prolong their therapeutic effect and adverse events (see sections CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS, *Drug Interactions*).

Darunavir and ritonavir are metabolized by CYP3A. Drugs that induce CYP3A activity would be expected to increase the clearance of darunavir and ritonavir, resulting in lowered plasma concentrations of darunavir and ritonavir. Co-administration of darunavir and ritonavir and other drugs that inhibit CYP3A may decrease the clearance of darunavir and ritonavir and may result in increased plasma concentrations of darunavir and ritonavir.

Drug interaction studies were performed with darunavir and other drugs likely to be co-administered and some drugs commonly used as probes for pharmacokinetic interactions. The effects of co-administration of darunavir on the AUC, C_{max}, and C_{min} values are summarized in Table 4 (effect of other drugs on darunavir) and Table 5 (effect of darunavir on other drugs). For information regarding clinical recommendations, see PRECAUTIONS, *Drug Interactions*.

Table 4: Drug Interactions: Pharmacokinetic Parameters for Darunavir in the Presence of Co-administered Drugs

Co-Administered Drug	Dose/Schedule		N	PK	LS Mean Ratio % (90% CI) of Darunavir Pharmacokinetic Parameters With/Without Co-administered Drug No Effect =1.00		
	Co-Administered Drug	Darunavir/ rtv			C_{max}	AUC	C_{min}
Co-Administration With Other Protease Inhibitors							
Atazanavir	300 mg q.d.^	400/100 mg b.i.d.†	13	↔	1.02 (0.96-1.09)	1.03 (0.94-1.12)	1.01 (0.88-1.16)
Indinavir	800 mg b.i.d.	400/100 mg b.i.d.	9	↑	1.11 (0.98-1.26)	1.24 (1.09-1.42)	1.44 (1.13-1.82)
Lopinavir/ Ritonavir	400/100 mg b.i.d.	300/100 mg b.i.d.	9	↓	0.61 (0.51-0.74)	0.47 (0.40-0.55)	0.35 (0.29-0.42)
Saquinavir hard gel capsule	1000 mg b.i.d.	400/100 mg b.i.d.	14	↓	0.83 (0.75-0.92)	0.74 (0.63-0.86)	0.58 (0.47-0.72)
Co-Administration With Other Antiretrovirals							
Efavirenz	600 mg q.d.	300/100 mg b.i.d.	12	↓	0.85 (0.72-1.00)	0.87 (0.75-1.01)	0.69 (0.54-0.87)
Nevirapine	200 mg b.i.d.	400/100 mg b.i.d.	8	↑	1.40‡ (1.14-1.73)	1.24‡ (0.97-1.57)	1.02‡ (0.79-1.32)
Tenofovir Disoproxil Fumarate	300 mg q.d.	300/100 mg b.i.d.	12	↑	1.16 (0.94-1.42)	1.21 (0.95-1.54)	1.24 (0.90-1.69)
Co-Administration With Other Drugs							
Clarithromycin	500 mg b.i.d.	400/100 mg b.i.d.	17	↔	0.83 (0.72-0.96)	0.87 (0.75-1.01)	1.01 (0.81-1.26)
Ketoconazole	200 mg b.i.d.	400/100 mg b.i.d.	14	↑	1.21 (1.04-1.40)	1.42 (1.23-1.65)	1.73 (1.39-2.14)
Omeprazole	20 mg q.d.	400/100 mg b.i.d.	16	↔	1.02 (0.95-1.09)	1.04 (0.96-1.13)	1.08 (0.93-1.25)
Paroxetine	20 mg q.d.	400/100 mg b.i.d.	16	↔	0.97 (0.92-1.02)	1.02 (0.95-1.10)	1.07 (0.96-1.19)
Ranitidine	150 mg b.i.d.	400/100 mg b.i.d.	16	↔	0.96 (0.89-1.05)	0.95 (0.90-1.01)	0.94 (0.90-0.99)
Sertraline	50 mg q.d.	400/100 mg b.i.d.	13	↔	1.01 (0.89-1.14)	0.98 (0.84-1.14)	0.94 (0.76-1.16)

N = number of subjects with data; - = no information available.
^ q.d. = daily
† b.i.d. = twice daily
‡ Ratio based on between-study comparison.

Table 5: Drug Interactions: Pharmacokinetic Parameters for Co-administered Drugs in the Presence of Darunavir/Ritonavir							
Co-Administered Drug	Dose/Schedule		N	PK	LS Mean Ratio % (90% CI) of Co-Administered Drug Pharmacokinetic Parameters With/Without Darunavir No effect =1.00		
	Co-Administered Drug	Darunavir/ rtv			C_{max}	AUC	C_{min}
Co-Administration With Other Protease Inhibitors							
Atazanavir	300 mg q.d.^ /100 mg RTV q.d. when administered alone 300 mg q.d. when administered with darunavir/ ritonavir	400/100 mg b.i.d. †	13	↔	0.89 (0.78-1.01)	1.08 (0.94-1.24)	1.52 (0.99-2.34)
Indinavir	800 mg b.i.d. /100 mg RTV b.i.d. when administered alone 800 mg b.i.d. when administered with darunavir/ ritonavir	400/100 mg b.i.d.	9	↑	1.08 (0.95-1.22)	1.23 (1.06-1.42)	2.25 (1.63-3.10)
Lopinavir/ Ritonavir	400/100 mg b.i.d.	300/100 mg b.i.d.	9	↑	1.22 (1.12-1.32)	1.37 (1.27-1.49)	1.72 (1.46-2.03)
Saquinavir hard gel capsule	1000 mg b.i.d. /100 mg RTV b.i.d. when administered alone 1000 mg b.i.d. when	400/100 mg b.i.d.	12	↔	0.94 (0.78-1.13)	0.94 (0.76-1.17)	0.82 (0.52-1.30)

	administered with darunavir/ ritonavir						
Co-Administration With Other Antiretrovirals							
Efavirenz	600 mg q.d.	300/100 mg b.i.d.	12	↑	1.15 (0.97-1.35)	1.21 (1.08-1.36)	1.17 (1.01-1.36)
Nevirapine	200 mg b.i.d.	400/100 mg b.i.d.	8	↑	1.18 (1.02-1.37)	1.27 (1.12-1.44)	1.47 (1.20-1.82)
Tenofovir Disoproxil Fumarate	300 mg q.d.	300/100 mg b.i.d.	12	↑	1.24 (1.08-1.42)	1.22 (1.10-1.35)	1.37 (1.19-1.57)

Co-Administration With Other Drugs							
Atorvastatin	40 mg q.d. when administered alone 10 mg q.d. when administered with darunavir/ ritonavir	300/100 mg b.i.d.	15	↑	0.56 (0.48-0.67)	0.85 (0.76-0.97)	1.81 (1.37-2.40)
Clarithromycin	500 mg b.i.d.	400/100 mg b.i.d.	17	↑	1.26 (1.03-1.54)	1.57 (1.35-1.84)	2.74 (2.30-3.26)
Ketoconazole	200 mg b.i.d.	400/100 mg b.i.d.	15	↑	2.11 (1.81-2.44)	3.12 (2.65-3.68)	9.68 (6.44-14.55)
Paroxetine	20 mg q.d.	400/100 mg b.i.d.	16	↓	0.64 (0.59-0.71)	0.61 (0.56-0.66)	0.63 (0.55-0.73)
Pravastatin	40 mg single dose	600/100 mg b.i.d.	14	↑	1.63 (0.95-2.82)	1.81 (1.23-2.66)	-
Sertraline	50 mg q.d.	400/100 mg b.i.d.	13	↓	0.56 (0.49-0.63)	0.51 (0.46-0.58)	0.51 (0.45-0.57)
Sildenafil	100 mg (single dose) administered alone 25 mg (single dose) when administered with darunavir/ ritonavir	400/100 mg b.i.d.	16	↑	0.62 (0.55-0.70)	0.97 (0.86-1.09)	-

N = number of subjects with data;- = no information available.
^ q.d. = daily
‡ b.i.d. = twice daily

INDICATIONS AND USAGE

PREZISTA, co-administered with 100 mg ritonavir (PREZISTA/rtv), and with other antiretroviral agents, is indicated for the treatment of human immunodeficiency virus (HIV) infection in

antiretroviral treatment-experienced adult patients, such as those with HIV-1 strains resistant to more than one protease inhibitor.

This indication is based on Week 24 analyses of plasma HIV RNA levels and CD4+ cell counts from 2 controlled trials of PREZISTA/rtv in combination with other antiretroviral drugs. Both studies were conducted in clinically advanced, treatment-experienced (NRTIs, NNRTIs, and PIs) adult patients with evidence of HIV-1 replication despite ongoing antiretroviral therapy.

The following points should be considered when initiating therapy with PREZISTA/rtv:

- Treatment history and, when available, genotypic or phenotypic testing, should guide the use of PREZISTA/rtv (see MICROBIOLOGY).

- The use of other active agents with PREZISTA/rtv is associated with a greater likelihood of treatment response (see MICROBIOLOGY and INDICATIONS AND USAGE, *Description of Clinical Studies*).

- The risks and benefits of PREZISTA/rtv have not been established in treatment-naïve adult patients or pediatric patients.

Description of Clinical Studies

The evidence of efficacy of PREZISTA/rtv is based on the analyses of 24-week data from 2 ongoing, randomized, controlled trials, TMC114-C213 and TMC114-C202, in antiretroviral treatment-experienced HIV-1 infected adult subjects. These efficacy results were supported by the 24-week pooled analysis of the open label trials TMC114-C215 and TMC114-C208 of subjects who initiated PREZISTA/rtv at the recommended dose.

Treatment-Experienced Subjects:

Studies TMC114-C213 and TMC114-C202: These are ongoing randomized, controlled, Phase 2b trials consisting of 2 parts: an initial partially-blinded, dose-finding part and a second long-term part in which all subjects randomized to PREZISTA/rtv received the recommended dose of 600/100 mg b.i.d.

HIV-1 infected subjects who were eligible for these trials had plasma HIV-1 RNA > 1000 copies/mL, had prior treatment with PI(s), NNRTI(s) and NRTI(s), had at least one primary PI mutation (D30N, M46I/L, G48V, I50L/V, V82A/F/S/T, I84V, L90M) at screening, and were on a stable PI-containing regimen at screening for at least 8 weeks. Randomization was stratified by the number of PI mutations, screening viral load, and the use of enfuvirtide. Analyses included 318 subjects in Study TMC114-C213 and 319 subjects in Study TMC114-C202 who had completed 24 weeks of treatment or discontinued earlier.

At 24 weeks, the virologic response rate was evaluated in subjects receiving PREZISTA/rtv plus an optimized background regimen (OBR) versus a control group receiving an investigator-selected PI(s) regimen plus an OBR. Prior to randomization, PI(s) and OBR were selected by the

investigator based on genotypic resistance testing and prior ARV history. The OBR consisted of at least 2 NRTIs with or without enfuvirtide. Selected PI(s) in the control arm included: lopinavir/ritonavir in 36%, (fos)amprenavir in 34%, saquinavir in 35% and atazanavir in 17%; 23% of the control subjects used dual-boosted PIs. Approximately 47% of all subjects used enfuvirtide, and 35% of the use was in subjects who were ENF-naïve. Virologic response was defined as a decrease in plasma HIV-1 RNA viral load of at least 1.0 $\log_{10}$ versus baseline.

In the pooled analysis for TMC114-C213 and TMC114-C202, demographics and baseline characteristics were balanced between the PREZISTA/rtv arm and the comparator PI arm. Table 6 compares the demographic characteristics between subjects in the PREZISTA/rtv 600/100 mg b.i.d. arm and subjects in the comparator PI arm.

Table 6: Demographic Characteristics of Subjects in the Studies TMC114-C213 and TMC114-C202 (Pooled Analysis)

	Randomized Studies TMC114-C213 and TMC114-C202	
	PREZISTA/rtv 600/100 mg b.i.d. + OBR N = 131	Comparator PI(s) + OBR N = 124
Demographic Characteristics		
Age (years) (range, years)	43.0 (27-73)	44.0 (25-65)
Sex		
Male	89%	88%
Female	11%	12%
Race		
White	81%	73%
Black	10%	15%
Hispanic	7%	8%
Median Baseline Plasma HIV-1 RNA ($\log_{10}$ copies/mL) (range, $\log_{10}$ copies/mL)	4.52 (3.0-6.4)	4.56 (2.2-6.1)
Median Baseline CD4+ Cell Count (cells/mm^3) (range, cells/mm^3)	153 (3-776)	163 (3-1274)
Percentage of Patients with Baseline Viral Load > 100,000 copies/mL	24.4%	29.0%
Percentage of Patients with Baseline CD4+ Cell Count < 200 cells/mm^3	67%	58%
Median Darunavir FC	4.3	3.3

Table 7 compares the baseline characteristics between subjects in the PREZISTA/rtv 600/100 mg b.i.d. arm and subjects in the comparator PI arm.

Table 7: Baseline Characteristics of Subjects in the Studies TMC114-C213 and TMC114-C202 (Pooled Analysis)

	Randomized Studies TMC114-C213 and TMC114-C202	
	PREZISTA/rtv 600/100 mg b.i.d. + OBR N = 131	Comparator PI(s) + OBR N = 124
Baseline Characteristics		
Median Number of Resistance-Associated:		
PI mutations^	8	8
NNRTI mutations	1	1
NRTI mutations	6	5
Percentage of Subjects with the following Baseline IAS Primary Protease Mutations†:		
≤ 1	8%	13%
2	37%	25%
≥ 3	54%	62%
Median Number of ARVs Previously Used‡:		
NRTIs	6	6
NNRTIs	1	1
PIs (excluding low-dose ritonavir)	5	5
Percentage of Subjects Resistant§ to All Available¶ PIs at Baseline, excluding Tipranavir	64%	61%
Percentage of Subjects with Prior Use of Enfuvirtide	19%	16%

^ L10F/I/R/V, K20I/L/M/R/T, L24I, D30N, V32I, L33F/I, M36I/L/V, M46I/L, I47A/V, G48V, I50L/V, F53L, I54A/L/M/S/T/V, A71V/T, G73A/C/S/T, V77I, V82A/F/L/S/T, I84A/C/V, N88D/S, L90M

† Based on the IAS-USA list of mutations (March 2005): D30N, L33F/I, M46I/L, G48V, I50L/V, V82A/F/L/S/T, I84A/C/V, L90M

‡ Only counting ARVs, excluding low-dose ritonavir, taken for at least 2 months, and for which start and stop dates were available

§ Based on phenotype (Antivirogram™)

¶ Commercially available PIs at the time of study enrollment

Week 24 outcomes for subjects on the recommended dose PREZISTA/rtv 600/100 mg b.i.d. from the pooled Studies TMC114-C213 and TMC114-C202 are shown in Table 8.

Table 8: Outcomes of Randomized Treatment Through Week 24 of the Studies TMC114-C213 and TMC114-C202 (Pooled Analysis)	
	Randomized Studies TMC114-C213 and TMC114-C202

	PREZISTA/rtv 600 mg b.i.d. + OBR N=131	Comparator PI + OBR N=124
Virologic Responders confirmed at least 1 $\log_{10}$ HIV-1 RNA below baseline through Week 24 (< 50 copies/mL at Week 24)	69.5% (45.0%)	21.0% (12.1%)
Virologic failures	26.0%	71.0%
Lack of initial response^	9.9%	57.3%
Rebound†	9.2%	9.7%
Never Suppressed‡	6.9%	4.0%
Death or discontinuation due to adverse events	3.9%	1.6%
Discontinuation due to other reasons	0.8%	6.5%

^ Subjects who did not achieve at least a confirmed 0.5 $\log_{10}$ HIV-1 RNA drop from baseline at Week 12

† Subjects with an initial response (confirmed 1 $\log_{10}$ drop in viral load), but without a confirmed 1 $\log_{10}$ drop in viral load at Week 24

‡Subjects who never reached a confirmed 1 $\log_{10}$ drop in viral load before Week 24

Through 24 weeks of treatment, the proportion of subjects with HIV-1 RNA < 400 copies/mL in the arm receiving PREZISTA/rtv 600/100 mg b.i.d. compared to the comparator PI arm was 63% and 19%, respectively. In addition, the mean changes in plasma HIV-1 RNA from baseline were -1.89 $\log_{10}$ copies/mL in the arm receiving PREZISTA/rtv 600/100 mg b.i.d. and -0.48 $\log_{10}$ copies/mL for the comparator PI arm. The mean increase from baseline in CD4+ cell counts was higher in the arm receiving PREZISTA/rtv 600/100 mg b.i.d. (92 cells/mm^3) than in the comparator PI arm (17 cells/mm^3).

The TMC114-C215/C208 analysis: Additional data on the efficacy of PREZISTA/rtv 600/100 mg b.i.d. have been obtained in treatment-experienced subjects participating in the non-randomized trials TMC114-C215 and TMC114-C208. The 246 subjects from these trials included in the TMC114-C215/C208 24-week efficacy analysis initiated therapy with PREZISTA/rtv with the recommended dose of 600/100 mg b.i.d. The OBR consisted of at least two NRTIs with or without enfuvirtide. Entry criteria for the TMC114-C215/C208 analysis were the same as those for Studies TMC114-C213 and TMC114-C202.

Baseline characteristics of the subjects included in the TMC114-C215/C208 analysis were comparable to those subjects in Studies TMC114-C213 and TMC114-C202.

The TMC114-C215/C208 24-week efficacy analysis supported the viral load reduction and CD4+ cell count increases observed in the Studies TMC114-C213 and TMC114-C202. Of the 246 subjects at Week 24, 65% had a virologic response defined as a decrease of at least 1.0 $\log_{10}$ in plasma viral load versus baseline and 40% of the subjects reached less than 50 HIV-1 RNA copies/mL. The

mean increase in CD4+ cell count versus baseline was 80 cells/mm^3 at Week 20. At Week 24, 57% of the subjects reached less than 400 HIV-1 RNA copies/mL, and the mean changes in plasma HIV-1 RNA from baseline were -1.65 log_{10} copies/mL.

CONTRAINDICATIONS

PREZISTA is contraindicated in patients with known hypersensitivity to any of the ingredients of the product.

Co-administration of PREZISTA/rtv is contraindicated with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events (narrow therapeutic index). These drugs are listed in Table 9 (also see PRECAUTIONS, *Drug Interactions*, Table 10).

Table 9: Drugs That Are Contraindicated With PREZISTA/rtv

Drug Class	Drugs Within Class That Are Contraindicated With PREZISTA/rtv
Antihistamines	Astemizole, Terfenadine
Ergot Derivatives	Dihydroergotamine, Ergonovine, Ergotamine, Methylergonovine
GI Motility Agent	Cisapride
Neuroleptic	Pimozide
Sedative/hypnotics	Midazolam, Triazolam

Due to the need for co-administration of PREZISTA with 100 mg of ritonavir, please refer to ritonavir prescribing information for a description of ritonavir contraindications.

WARNINGS

ALERT: Find out about medicines that should not be taken with PREZISTA/rtv. This statement is included on the product's bottle label.

General

PREZISTA (darunavir) must be co-administered with ritonavir and food to exert its therapeutic effect (see DOSAGE and ADMINISTRATION). Failure to correctly administer PREZISTA with ritonavir and food will result in reduced plasma concentrations of darunavir that will be insufficient to achieve the desired antiviral effect.

Please refer to ritonavir prescribing information for additional information on precautionary measures.

Skin Rash

During the clinical development program, severe skin rash, including erythema multiforme and Stevens-Johnson Syndrome, has been reported. In some cases, fever and elevations of transaminases have also been reported. In clinical trials (n=924), rash (all grades, regardless of causality) occurred in 7% of subjects treated with PREZISTA; the discontinuation rate due to rash was 0.3%. Rashes were generally mild-to-moderate, self-limited maculopapular skin eruptions. Treatment with PREZISTA should be discontinued if severe rash develops.

Sulfa Allergy
Darunavir contains a sulfonamide moiety. PREZISTA (darunavir) should be used with caution in patients with a known sulfonamide allergy.

Drug Interactions
PREZISTA and ritonavir are both inhibitors of CYP3A. Co-administration of PREZISTA/rtv with drugs primarily metabolized by CYP3A may result in increased plasma concentrations of such drugs, which could increase or prolong their therapeutic effect and adverse events (see sections CONTRAINDICATIONS and PRECAUTIONS, *Drug Interactions*).

Diabetes Mellitus / Hyperglycemia
New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and hyperglycemia have been reported during postmarketing surveillance in HIV-infected patients receiving protease inhibitor therapy. Some patients required either initiation or dose adjustments of insulin or oral hypoglycemic agents for treatment of these events. In some cases, diabetic ketoacidosis has occurred. In those patients who discontinued protease inhibitor therapy, hyperglycemia persisted in some cases. Because these events have been reported voluntarily during clinical practice, estimates of frequency cannot be made and causal relationships between protease inhibitor therapy and these events have not been established.

PRECAUTIONS

Patients with co-existing conditions
Hepatic Impairment: Darunavir is primarily metabolized by the liver, hence, caution should be exercised when PREZISTA/rtv is given to patients with hepatic impairment, because increased plasma concentrations are expected in patients with hepatic impairment. There are no data regarding the use of PREZISTA/rtv when co-administered to patients with varying degrees of hepatic impairment; therefore, specific dosage recommendations cannot be made. PREZISTA/rtv should be used with caution in patients with hepatic impairment (see CLINICAL PHARMACOLOGY, *Pharmacokinetics in Adults*, *Special Populations*, *Hepatic Impairment* and DOSAGE AND ADMINISTRATION).

Patients with pre-existing liver dysfunction, including chronic active hepatitis, can have an increased frequency of liver function abnormalities during combination antiretroviral therapy and should be monitored according to standard practice. If there is evidence of worsening of liver disease in such patients, interruption or discontinuation of treatment must be considered.

Renal Impairment: Population pharmacokinetic analysis showed that the pharmacokinetics of darunavir were not significantly affected in HIV infected subjects with moderate renal impairment (CrCL between 30-60 mL/min, n=20). There are no pharmacokinetic data available in HIV-1 infected patients with severe renal impairment or end stage renal disease; however, since the renal clearance of darunavir is limited, a decrease in total body clearance is not expected in patients with renal impairment. As darunavir and ritonavir are highly bound to plasma proteins, it is unlikely that they will be significantly removed by hemodialysis or peritoneal dialysis (see CLINICAL PHARMACOLOGY, *Pharmacokinetics in Adults*, *Special Populations*, *Renal Impairment* and DOSAGE AND ADMINISTRATION).

Hemophilia: There have been reports of increased bleeding, including spontaneous skin hematomas and hemarthrosis in patients with hemophilia type A and B treated with protease inhibitors. In some patients, additional factor VIII was given. In more than half of the reported cases, treatment with protease inhibitors was continued or reintroduced if treatment had been discontinued. A causal relationship between protease inhibitor therapy and these episodes has not been established.

Fat Redistribution
Redistribution/accumulation of body fat, including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

Immune Reconstitution Syndrome
During the initial phase of treatment, patients responding to antiretroviral therapy may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* complex, cytomegalovirus, *Pneumocystis jeroveci* pneumonia, and tuberculosis), which may necessitate further evaluation and treatment.

Resistance/Cross-Resistance
Because the potential for HIV cross-resistance among protease inhibitors has not been fully explored in PREZISTA/rtv treated patients, it is unknown what effect therapy with PREZISTA will have on the activity of subsequently administered protease inhibitors.

Information for Patients
A statement to patients and healthcare providers is included on the product's bottle label: **ALERT: Find out about medicines that should NOT be taken with PREZISTA.** A Patient Package Insert for PREZISTA is available for patient information.

Patients should be informed that PREZISTA is not a cure for HIV infection and that they may continue to develop opportunistic infections and other complications associated with HIV disease. The long-term effects of PREZISTA are unknown at this time. Patients should be told that there are currently no data demonstrating that therapy with PREZISTA can reduce the risk of transmitting HIV to others.

Patients should be told that sustained decreases in plasma HIV RNA have been associated with a reduced risk of progression to AIDS and death. Patients should remain under the care of a physician while using PREZISTA.

Patients should be advised to take PREZISTA and ritonavir (NORVIR®) with food every day as prescribed. The type of food does not affect exposure to PREZISTA. Patients should be instructed to swallow whole tablets with a drink such as water or milk. PREZISTA must always be used with 100 mg of ritonavir (NORVIR®) in combination with other antiretroviral drugs. Patients should not alter the dose of either PREZISTA or ritonavir (NORVIR®), discontinue ritonavir (NORVIR®), or discontinue therapy with PREZISTA without consulting their physician. If a patient misses a dose of PREZISTA or ritonavir (NORVIR®) by more than 6 hours, the patient should be told to wait and then take the next dose of PREZISTA and ritonavir (NORVIR®) at the regularly scheduled time. If the patient misses a dose of PREZISTA or ritonavir (NORVIR®) by less than 6 hours, the patient should be told to take PREZISTA and ritonavir (NORVIR®) immediately, and then take the next

dose of PREZISTA and ritonavir (NORVIR®) at the regularly scheduled time. If a dose of PREZISTA or ritonavir (NORVIR®) is skipped, the patient should not double the next dose. Inform the patient that he or she should not take more or less than the prescribed dose of PREZISTA or ritonavir (NORVIR®) at any one time.

PREZISTA/rtv may interact with many drugs; therefore, patients should be advised to report to their healthcare provider the use of any other prescription or nonprescription medication or herbal products, including St. John's wort.

Patients receiving estrogen-based contraceptives should be instructed to use alternate contraceptive measures during therapy with PREZISTA/rtv because hormonal levels may decrease.

Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy, including PREZISTA/rtv, and that the cause and long-term health effects of these conditions are not known at this time.

Drug Interactions
PREZISTA and ritonavir are both inhibitors of CYP3A. Co-administration of PREZISTA and ritonavir with drugs that are primarily metabolized by CYP3A may result in increased plasma concentrations of such drugs, which could increase or prolong their therapeutic effect and adverse events (see Tables 10 and 11).

Drugs that are contraindicated and not recommended for co-administration with PREZISTA/rtv are included in Table 10. These recommendations are based on either drug interaction studies or predicted interactions due to the expected magnitude of interaction and potential for serious events or loss of efficacy.

Table 10: Drugs That Should Not Be Co-administered With PREZISTA/rtv

Drug Class: Drug Name	Clinical Comment
Anticonvulsants: carbamazepine, phenobarbital, phenytoin	Carbamazepine, phenobarbital and phenytoin are inducers of CYP450 enzymes. PREZISTA/rtv should not be used in combination with phenobarbital, phenytoin, or carbamazepine as co-administration may cause significant decreases in darunavir plasma concentrations. This may result in loss of therapeutic

	effect to PREZISTA.
Antihistamines: astemizole, terfenadine	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Antimycobacterial: rifampin	Rifampin is a potent inducer of CYP450 metabolism. PREZISTA/rtv should not be used in combination with rifampin, as this may cause significant decreases in darunavir plasma concentrations. This may result in loss of therapeutic effect to PREZISTA.
Ergot Derivatives: dihydroergotamine, ergonovine, ergotamine, methylergonovine	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
Gastrointestinal Motility Agent: cisapride	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Herbal Products: St. John's wort (*Hypericum perforatum*)	PREZISTA/rtv should not be used concomitantly with products containing St. John's wort (*Hypericum perforatum)* because co-administration may cause significant decreases in darunavir plasma concentrations. This may result in loss of therapeutic effect to PREZISTA.
HMG-CoA Reductase Inhibitors: lovastatin, simvastatin	Potential for serious reactions such as risk of myopathy including rhabdomyolysis. For dosing recommendation regarding atorvastatin and pravastatin, see Table 11: Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction.
Neuroleptic: pimozide	CONTRAINDICATED due to the potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Sedative/Hypnotics:	CONTRAINDICATED due to potential for serious

midazolam, triazolam	and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.

Table 11: Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction (See CLINICAL PHARMACOLOGY for Magnitude of Interaction, Tables 4 and 5)

Concomitant Drug Class: Drug Name	Effect on Concentration of Darunavir or Concomitant Drug	Clinical Comment
HIV-Antiviral Agents: Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)		

Efavirenz	↓ darunavir ↑ efavirenz	Co-administration of darunavir/rtv and efavirenz decreased darunavir AUC by 13% and C_{min} by 31%. The AUC of efavirenz increased by 21% and C_{min} increased by 17%. The clinical significance has not been established. The combination of PREZISTA/rtv and efavirenz should be used with caution.
Nevirapine	↔ darunavir ↑ nevirapine	PREZISTA/rtv and nevirapine can be co-administered without any dose adjustments.
HIV-Antiviral Agents: Nucleoside Reverse Transcriptase Inhibitors (NRTIs)		
Didanosine		It is recommended that didanosine be administered on an empty stomach. Therefore, didanosine should be administered one hour before or two hours after PREZISTA/rtv (which are administered with food).
Tenofovir Disoproxil Fumarate	↔ darunavir ↑ tenofovir	PREZISTA/rtv and tenofovir disoproxil fumarate can be co-administered without any dose adjustments.
HIV-Antiviral Agents: HIV-Protease Inhibitors (PIs)		
Atazanavir (The reference regimen for atazanavir was atazanavir/ritonavir 300/100 mg q.d.)	↔ darunavir ↔ atazanavir	PREZISTA/rtv and atazanavir (300 mg q.d.) can be co-administered.
Indinavir	↑ darunavir	The appropriate dose of

(The reference regimen for indinavir was indinavir/ritonavir 800/100 mg b.i.d.)	↑ indinavir	indinavir in combination with PREZISTA/rtv has not been established.
Lopinavir/ritonavir	↓ darunavir ↑ lopinavir	Due to decrease in the exposure (AUC) of darunavir by 53%, appropriate doses of the combination have not been established. Hence, it is not recommended to co-administer lopinavir/ritonavir and PREZISTA, with or without an additional low-dose of ritonavir.
Saquinavir	↓ darunavir ↔ saquinavir	Due to a decrease in the exposure (AUC) of darunavir by 26%, appropriate doses of the combination have not been established. Hence, it is not recommended to co-administer saquinavir and PREZISTA, with or without low-dose ritonavir.
Other Agents		
Antiarrhythmics: bepridil, lidocaine (systemic), quinidine, amiodarone	↑ antiarrhythmics	Concentrations of bepridil, lidocaine, quinidine and amiodarone may be increased when co-administered with PREZISTA/rtv. Caution is warranted and therapeutic concentration monitoring, if available, is recommended for antiarrhythmics when co-administered with PREZISTA/rtv.
Anticoagulant:	↓ warfarin	Warfarin concentrations

warfarin	↔ darunavir	may be affected when co-administered with PREZISTA/rtv. It is recommended that the international normalized ratio (INR) be monitored when warfarin is combined with PREZISTA/rtv.
Antidepressant: trazodone	↑ trazodone	Concomitant use of trazodone and PREZISTA/rtv may increase plasma concentrations of trazodone. Adverse events of nausea, dizziness, hypotension and syncope have been observed following co-administration of trazodone and ritonavir. If trazodone is used with a CYP3A inhibitor such as PREZISTA/rtv, the combination should be used with caution and a lower dose of trazodone should be considered.
Anti-infective: clarithromycin	↑ clarithromycin	No dose adjustment of darunavir or clarithromycin is required for patients with normal renal function. For patients with renal impairment, the following dose adjustments should be considered: • For subjects with CLcr of 30-60 mL/min, the dose of clarithromycin should be reduced by 50%.

		• For subjects with CLcr of < 30 mL/min, the dose of clarithromycin should be reduced by 75%.
Antifungals: ketoconazole, itraconazole, voriconazole	↑ ketoconazole ↑ darunavir ↑ itraconazole (not studied) ↓ voriconazole (not studied)	Ketoconazole and itraconazole are potent inhibitors as well as substrates of CYP3A. Concomitant systemic use of ketoconazole, itraconazole, and darunavir/ritonavir may increase plasma concentration of darunavir. Plasma concentrations of ketoconazole or itraconazole may be increased in the presence of darunavir/ritonavir. When co-administration is required, the daily dose of ketoconazole or itraconazole should not exceed 200 mg. Co-administration of voriconazole with darunavir/ritonavir has not been studied. Administration of voriconazole with ritonavir (100 mg twice daily) decreased the AUC of voriconazole by an average of 39%. Voriconazole should not be administered to patients receiving darunavir/ritonavir unless an assessment of the benefit/risk ratio justifies the use of voriconazole.

Antimycobacterial: rifabutin	↑ rifabutin ↓ darunavir	Rifabutin is an inducer and substrate of CYP450 enzymes. Concomitant use of rifabutin and darunavir in the presence of ritonavir is expected to increase rifabutin plasma concentrations and decrease darunavir plasma concentrations. When indicated, it is recommended to administer rifabutin at a dosage of 150 mg once every other day when co-administered with PREZISTA/rtv.
Calcium Channel Blockers: felodipine, nifedipine, nicardipine	↑ calcium channel blockers	Plasma concentrations of calcium channel blockers (e.g. felodipine, nifedipine, nicardipine) may increase when PREZISTA/rtv are co-administered. Caution is warranted and clinical monitoring of patients is recommended.
Corticosteroid: dexamethasone fluticasone propionate	↓ darunavir ↑ fluticasone propionate	Use with caution. Systemic dexamethasone induces CYP3A and can thereby decrease darunavir plasma concentrations. This may result in loss of therapeutic effect to PREZISTA. Concomitant use of inhaled fluticasone propionate and PREZISTA/rtv may increase plasma concentrations of fluticasone propionate. Alternatives should be considered, particularly for

		long term use.
HMG-CoA Reductase Inhibitors: atorvastatin, pravastatin	↑ atorvastatin ↑ pravastatin	When atorvastatin and PREZISTA/rtv is co-administered, it is recommended to start with the lowest possible dose of atorvastatin with careful monitoring. A gradual dose increase of atorvastatin may be considered based on the clinical response. When PREZISTA/rtv was administered with pravastatin, the mean increase in pravastatin AUC was 81%. However, pravastatin AUC increased by up to 5-fold in some subjects. The mechanism of the interaction is not known.
H2-Receptor Antagonists and Proton Pump Inhibitors: omeprazole, ranitidine	↔ darunavir	PREZISTA/rtv can be co-administered with H2-receptor antagonists and proton pump inhibitors without any dose adjustments.
Immunosuppressants: cyclosporine, tacrolimus, sirolimus	↑ immunosuppressants	Plasma concentrations of cyclosporine, tacrolimus or sirolimus may be increased when co-administered with PREZISTA/rtv. Therapeutic concentration monitoring of the immunosuppressive agent is recommended for immunosuppressant agents when co-administered with PREZISTA/rtv.
Narcotic Analgesic: methadone	↓ methadone	When methadone is co-administered with

		PREZISTA/rtv, patients should be monitored for opiate abstinence syndrome, as ritonavir is known to induce the metabolism of methadone, leading to a decrease in its plasma concentrations. An increase in methadone dosage may be considered based on the clinical response.
Oral Contraceptives/estrogen: ethinyl estradiol norethindrone	↓ ethinyl estradiol ↓ norethindrone	Plasma concentrations of ethinyl estradiol may be decreased due to induction of its metabolism by ritonavir. Alternative or additional contraceptive measures should be used when estrogen-based contraceptives are co-administered with PREZISTA/rtv.
PDE-5 inhibitors: sildenafil, vardenafil, tadalafil	↑ PDE-5 inhibitors	Concomitant use of PDE-5 inhibitors with PREZISTA/rtv should be done with caution. If concomitant use of PREZISTA/rtv with sildenafil, vardenafil, or tadalafil is required, sildenafil at a single dose not exceeding 25 mg in 48 hours, vardenafil at a single dose not exceeding 2.5 mg dose in 72 hours, or tadalafil at a single dose not exceeding 10 mg dose in 72 hours, is recommended.
Selective Serotonin Reuptake	↔ darunavir	If sertraline or paroxetine

Inhibitors (SSRIs): sertraline, paroxetine	↓ sertraline ↓ paroxetine	is co-administered with PREZISTA/rtv, the recommended approach is a careful dose titration of the SSRI based on a clinical assessment of antidepressant response. In addition, patients on a stable dose of sertraline or paroxetine who start treatment with PREZISTA/rtv should be monitored for antidepressant response.

Other NRTIs:
Based on the different elimination pathways of the other NRTIs (zidovudine, zalcitabine, emtricitabine, stavudine, lamivudine and abacavir) that are primarily renally excreted, no drug interactions are expected for these drugs and PREZISTA/rtv.

Other protease inhibitors:
The co-administration of PREZISTA/rtv and PIs other than lopinavir/ritonavir, saquinavir, atazanavir, and indinavir has not been studied. Therefore, such co-administration is not recommended.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis and Mutagenesis:
Long-term carcinogenicity studies of darunavir in rodents have not been completed. Darunavir, however, was tested negative in the *in vitro* Ames reverse mutation assay and *in vitro* chromosomal aberration assay in human lymphocytes, both tested in the absence and presence of metabolic activation system. Darunavir does not induce chromosomal damage in the *in vivo* micronucleus test in mice.

Impairment of Fertility:
There were no effects on fertility and early embryonic development with darunavir in rats and darunavir has shown no teratogenic potential in mice (in the presence or absence of ritonavir), rats and rabbits.

Pregnancy
Pregnancy Category B: Reproduction studies conducted with darunavir have shown no embryotoxicity or teratogenicity in mice, rats and rabbits. Because of limited bioavailability of darunavir in animals and/or dosing limitations, the plasma exposures (AUC values) were approximately 50% in mice and rats and 5% in the rabbit of those obtained in humans at the recommended clinical dose boosted with ritonavir.

In the rat pre- and postnatal development study, a reduction in pup body weight gain was observed with darunavir alone or in combination with ritonavir during lactation. This was due to exposure of pups to drug substances via the milk. Sexual development, fertility or mating performance of offspring was not affected by maternal treatment with darunavir alone or in combination with ritonavir. The maximal plasma exposures achieved in rats were approximately 50% of those obtained in humans at the recommended clinical dose boosted with ritonavir.

There are, however, no adequate and well-controlled studies in pregnant women. PREZISTA should be used during pregnancy only if the potential benefit justifies the potential risk.

Antiretroviral Pregnancy Registry: *To monitor maternal-fetal outcomes of pregnant women exposed to PREZISTA, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.*

Nursing Mothers
The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV. Although it is not known whether darunavir is secreted in human milk, darunavir is secreted into the milk of lactating rats. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breastfeed if they are receiving PREZISTA.**

Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

Geriatric Use
Clinical studies of PREZISTA did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. In general, caution should be exercised in the administration and monitoring of PREZISTA in elderly patients reflecting the greater frequency of decreased hepatic function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

The safety assessment is based on all safety data from the Studies TMC114-C213 and TMC114-C202 and the TMC114-C215/C208 analysis reported with the recommended dose PREZISTA/rtv 600/100 mg b.i.d. in the 458 subjects who initiated treatment with the recommended dose (*de novo* subjects). In Studies TMC114-C213 and TMC114-C202, the mean exposure in weeks for subjects in the PREZISTA/rtv 600/100 mg b.i.d. arm and comparator PI arm was 63.5 and 31.5, respectively. The mean exposure in weeks for subjects in the TMC114-C215/C208 analysis was 23.9.

The most common treatment-emergent adverse events (> 10%) reported in the *de novo* subjects, regardless of causality or frequency, were diarrhea, nausea, headache, and nasopharyngitis.

For subjects in the PREZISTA/rtv 600/100 mg b.i.d. arm and the comparator PI arm in the pooled analysis for Studies TMC114-C213 and TMC114-C202, diarrhea was reported in 19.8% and 28.2%, nausea in 18.3% and 12.9%, headache in 15.3% and 20.2%, and nasopharyngitis in 13.7% and 10.5%, of subjects, respectively. In the randomized trials, rates of discontinuation of therapy

due to adverse events were 9% in subjects receiving PREZISTA/rtv and in 5% of subjects in the comparator PI arm.

Due to the need for co-administration of PREZISTA with 100 mg of ritonavir, please refer to ritonavir prescribing information for ritonavir-associated adverse reactions.

Drug-related clinical adverse events of moderate or severe intensity (≥ Grade 2) occurring in ≥ 2% of subjects treated with PREZISTA/rtv for 1 to 96 weeks are presented in Table 12.

Table 12: Percentage of Subjects with Selected Treatment Emergent, Drug-Related^ Adverse Events of at least Moderate Intensity (Grades 2-4) in ≥ 2% of Adult Subjects in Any PREZISTA/rtv Treatment Groups†

System Organ Class, Preferred Term, %	Randomized Studies TMC114-C213 and TMC114-C202		Non-randomized TMC114-C215/C208 Analysis
	PREZISTA/rtv 600/100 mg b.i.d. +OBR N = 131	Comparator PI +OBR N = 124	PREZISTA/rtv 600/100 mg b.i.d. +OBR N = 327
Gastrointestinal Disorders			
Diarrhea	2.3%	3.2%	2.8%
Vomiting	1.5%	1.6%	2.4%
Abdominal Pain	2.3%	0.8%	1.2%
Constipation	2.3%	0.8%	0.6%
Nervous System Disorders			
Headache	3.8%	2.4%	0.9%

^ Includes adverse events at least possibly, probably, or very likely related to the drug
N=total number of subjects per treatment group
† Excludes laboratory abnormalities that were reported as Adverse Events (see Table 13: Treatment Emergent Grade 2 to 4 Laboratory Abnormalities Reported in ≥ 2% of Subjects)

Treatment-emergent adverse events occurring in less than 2% of *de novo* subjects (n=458) receiving PREZISTA/rtv, considered at least possibly related to treatment and of at least moderate intensity are listed below by body system:

Body as a Whole:
folliculitis, asthenia, pyrexia, fatigue, rigors, hyperthermia, peripheral edema

Cardiovascular System:
myocardial infarction, tachycardia, hypertension

Digestive System:
flatulence, abdominal distension, dry mouth, dyspepsia, abdominal pain, nausea, constipation

Metabolic and Nutritional Disorders:
anorexia, hypercholesterolemia, hyperlipidemia, diabetes mellitus, decreased appetite, obesity, fat redistribution, hyponatremia, polydipsia

Musculoskeletal System:
arthralgia, pain in extremity, myalgia, osteopenia, osteoporosis

Nervous System:
peripheral neuropathy, hypoesthesia, memory impairment, paresthesia, somnolence, transient ischemic attack, confusional state, disorientation, irritability, altered mood, nightmare, anxiety, headache

Respiratory System:
dyspnea, cough, hiccups

Skin and Appendages:
lipoatrophy, night sweats, allergic dermatitis, eczema, toxic skin eruption, alopecia, dermatitis medicamentosa, hyperhidrosis, skin inflammation, maculopapular rash, erythema multiforme, Stevens-Johnson Syndrome (reported in another ongoing clinical study)

Special Senses:
vertigo

Urogenital System:
acute renal failure, renal insufficiency, nephrolothiasis, polyuria, gynecomastia

Laboratory abnormalities:
The percentages of adult subjects treated with PREZISTA/rtv 600/100 mg b.i.d. with treatment-emergent Grade 2 to 4 laboratory abnormalities are presented in Table 13.

Table 13: Treatment Emergent Grade 2 to 4 Laboratory Abnormalities Reported in ≥ 2% of Subjects

		Randomized Studies TMC114-C213 and TMC114-C202		**Non-randomized TMC114-C215/C208 Analysis**
Laboratory Parameter Preferred Term, %	**Limit**	**PREZISTA/ rtv 600/100 mg b.i.d. + OBR N = 131**	**Comparator PI + OBR N = 124**	**PREZISTA/ rtv 600/100 mg b.i.d. N = 327**
Biochemistry				
Aspartate	> 2.5 X ULN	10.0%	13.0%	5.3%

Aminotransferase				
Alanine Aminotransferase	> 2.5 X ULN	6.9%	9.8%	5.6%
Gamma Glutamyl Transferase	> 2.5 X ULN	9.2%	8.9%	8.4%
Hyperbilirubinemia	> 1.5 X ULN	2.3%	15.4%	0.9%
Alkaline Phosphatase	> 2.5 X ULN	4.6%	0%	2.8%
Pancreatic Amylase	> 1.5 X ULN	16.9%	8.9%	10.8%
Pancreatic Lipase	> 1.5 X ULN	8.5%	4.1%	6.2%
Hyperglycemia	≥ 161 mg/dL	2.3%	8.1%	5.9%
Hypoglycemia	≤ 54 mg/dL	1.5%	1.6%	3.7%
Total Cholesterol	≥ 240 mg/dL	9.2%	3.3%	8.0%
Triglycerides	> 400 mg/dL	25.4%	26.0%	18.9%
Hypoalbuminemia	< 3 g/dL	3.1%	1.6%	4.3%
Hyperuricemia	≥ 9.9 mg/dL	6.9%	6.5%	2.2%
Bicarbonate	< 15 mmol/L	3.1%	4.1%	3.4%
Hypocalcemia	≤ 7.8 mg/dL	0%	0.8%	4.0%
Hyponatremia	≤ 129 meq/L	0.8%	0%	2.5%
Hypernatremia	≥ 151 meq/L	2.3%	0%	0%
Hematology				
White Blood Cell Count decrease	< 3000 count/mm^3	15.4%	18.7%	13.0%
Total Absolute Neutrophil Count decrease	≤ 999 mm^3	6.9%	9.8%	11.5%
Lymphocytes decrease	< 1000 count/mm^3	4.6%	19.5%	10.9%
Partial Thromboplastin Time increase	> 1.66 X ULN	7.8%	4.1%	4.3%
Plasma Prothrombin Time increase	> 1.25 X ULN	3.9%	0.8%	0.6%
Platelet Count decrease	< 75,000/mm^3	3.1%	1.6%	2.8%

Patients co-infected with hepatitis B and/or hepatitis C virus:
Subjects co-infected with hepatitis B or C virus receiving PREZISTA/rtv, did not experience higher incidence of adverse events or clinical chemistry abnormalities than subjects receiving PREZISTA/rtv who were not co-infected. The pharmacokinetic exposure in co-infected subjects was comparable to that in subjects without co-infection. Standard clinical monitoring of patients with chronic hepatitis B and/or C is considered adequate.

OVERDOSAGE

Human experience of acute overdose with PREZISTA/rtv is limited. Single doses up to 3200 mg of the oral solution of darunavir alone and up to 1600 mg of the tablet formulation of darunavir in combination with ritonavir have been administered to healthy volunteers without untoward symptomatic effects.

There is no specific antidote for overdose with PREZISTA. Treatment of overdose with PREZISTA consists of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. If indicated, elimination of unabsorbed active substance is to be achieved by emesis or gastric lavage. Administration of activated charcoal may also be used to aid in removal of unabsorbed active substance. Since PREZISTA is highly protein bound, dialysis is unlikely to be beneficial in significant removal of the active substance.

DOSAGE AND ADMINISTRATION

Adults: The recommended oral dose of PREZISTA tablets is 600 mg (two 300 mg tablets) twice daily taken with ritonavir 100 mg twice daily and with food. The type of food does not affect exposure to darunavir.

Pediatric Patients: The safety and efficacy of PREZISTA in pediatric patients has not been established (see CLINICAL PHARMACOLOGY, *Special Populations, Pediatric Patients*).

Hepatic Impairment: There are no data regarding the use of PREZISTA/rtv when co-administered to patients with varying degrees of hepatic impairment; therefore, specific dosage recommendations cannot be made. PREZISTA/rtv should be used with caution in patients with hepatic impairment (see CLINICAL PHARMACOLOGY, *Pharmacokinetics in Adults, Special Populations, Hepatic Impairment* and PRECAUTIONS, *Patients with co-existing conditions, Hepatic Impairment*).

Renal Impairment: No dose adjustment is required in patients with moderate renal impairment. There are no pharmacokinetic data available in HIV-1 infected patients with severe renal impairment or end stage renal disease (see CLINICAL PHARMACOLOGY, *Pharmacokinetics in Adults, Special Populations, Renal Impairment* and PRECAUTIONS, *Patients with co-existing conditions, Renal Impairment*).

HOW SUPPLIED

PREZISTA (darunavir) tablets are supplied as orange, oval-shaped, film-coated tablets containing darunavir ethanolate equivalent to 300 mg of darunavir per tablet. Each tablet is debossed with "300" on one side and "TMC114" on the other side. PREZISTA tablets are packaged in bottles in the following configuration:

300 mg tablets—bottles of 120 (NDC 59676-560-01)

Storage:
Store PREZISTA tablets at 25°C (77°F); with excursions permitted to 15°-30°C (59°-86°F).

Rx Only

Manufactured for Tibotec, Inc. by:
JOLLC, Gurabo, Puerto Rico
Distributed by:
Tibotec Therapeutics, Division of Ortho Biotech Products, L.P., Raritan NJ 08869

Patent Numbers: 5,843,946; 6,248,775; 6,335,460 and other US patents pending

 Issued: June 2006

10101700

PREZISTA™* (darunavir) Tablets

Patient Information about
PREZISTA (pre-ZIS-ta)
for HIV (Human Immunodeficiency Virus) Infection
Generic name: darunavir (da-ROO-nuh-veer)

ALERT: Find out about medicines that should NOT be taken with PREZISTA. Please also read the section "Who should not take PREZISTA?".

Please read this information before you start taking PREZISTA. Also, read the leaflet each time you renew your prescription, just in case anything has changed. Remember, this leaflet does not take the place of careful discussions with your doctor. You and your doctor should discuss your treatment with PREZISTA the first time you take your medicine and at regular checkups. You should remain under a doctor's care when using PREZISTA and should not change or stop treatment without first talking with a doctor.

WHAT IS PREZISTA?

PREZISTA is an oral tablet used for the treatment of HIV (Human Immunodeficiency Virus) infection in adults. HIV is the virus that causes AIDS (Acquired Immune Deficiency Syndrome). PREZISTA is a type of anti-HIV drug called a protease (PRO-tee-ase) inhibitor.

HOW DOES PREZISTA WORK?

PREZISTA blocks HIV protease, an enzyme which is needed for HIV to multiply. When used with other anti-HIV medicines, PREZISTA may reduce the amount of HIV in your blood (called "viral load") and increase your CD4 (T) cell count. HIV infection destroys CD4 (T) cells, which are important to the immune system. The immune system helps fight infection. Reducing the amount of HIV and increasing the CD4 (T) cell count may improve your immune system and, thus, reduce the risk of death or infections that can happen when your immune system is weak (opportunistic infections).

PREZISTA is always taken with and at the same time as 100 mg of ritonavir (NORVIR®), in combination with other anti-HIV medicines. PREZISTA should also be taken with food.

DOES PREZISTA CURE HIV OR AIDS?

PREZISTA does **not** cure HIV infection or AIDS. At present, there is no cure for HIV infection. People taking PREZISTA may still develop infections or other conditions associated with HIV infection. Because of this, it is very important for you to remain under the care of a doctor. Although PREZISTA is not a cure for HIV or AIDS, PREZISTA can help reduce your risks of getting illnesses associated with HIV infection (AIDS and opportunistic infection) and eventually dying from these conditions.

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*Trademark of Tibotec, Inc.

DOES PREZISTA REDUCE THE RISK OF PASSING HIV TO OTHERS?

PREZISTA does **not** reduce the risk of passing HIV to others through sexual contact, sharing needles, or being exposed to your blood. For your health and the health of others, it is important to always practice safer sex by using a latex or polyurethane condom or other barrier method to lower the chance of sexual contact with any body fluids such as semen, vaginal secretions, or blood. Never re-use or share needles.

Ask your doctor if you have any questions on how to prevent passing HIV to other people.

WHAT SHOULD I TELL MY DOCTOR BEFORE I TAKE PREZISTA?

Tell your doctor about all of your medical conditions, including if you:

- are allergic to sulfa medicines.
- have diabetes. In general, anti-HIV medicines, such as PREZISTA, might increase sugar levels in the blood.
- have liver problems.
- have hemophilia. Anti-HIV medicines, such as PREZISTA, might increase the risk of bleeding.
- are pregnant or planning to become pregnant. The effects of PREZISTA on pregnant women or their unborn babies are not known. You and your doctor will need to decide if taking PREZISTA is right for you. If you take PREZISTA while you are pregnant, talk to your doctor about how you can be included in the Antiretroviral Pregnancy Registry.
- are breastfeeding. Do not breastfeed if you are taking PREZISTA. You should not breastfeed if you have HIV because of the chance of passing HIV to your baby. Talk with your doctor about the best way to feed your baby.

WHO SHOULD NOT TAKE PREZISTA?**

Together with your doctor, you need to decide whether taking PREZISTA is right for you.

Do not take PREZISTA if you:

- are allergic to darunavir or any of the other ingredients in PREZISTA
- are allergic to ritonavir (NORVIR®)
- take any of the following types of medicines because you could experience serious side effects:

Type of Drug	Examples of Generic Names (Brand Names)
Antihistamines (to treat allergy symptoms)	astemizole (Hismanal®) terfenadine (Seldane®)
Ergot Derivatives (to treat migraine and headaches)	dihydroergotamine (D.H.E. 45®, Migranal®) ergonovine ergotamine (Wigraine®, Ergostat®, Cafergot®, Ergomar®) methylergonovine
Gastrointestinal Motility Agent (to treat some digestive conditions)	cisapride (Propulsid®)
Neuroleptic (to treat psychiatric conditions)	pimozide (Orap®)
Sedative/hypnotics (to treat trouble with sleeping and/or anxiety)	midazolam (Versed®) triazolam (Halcion®)

CAN PREZISTA BE TAKEN WITH OTHER MEDICATIONS?**

Tell your doctor about all the medicines you take including prescription and nonprescription medicines, vitamins, and herbal supplements, including St. John's wort (*Hypericum perforatum*). PREZISTA and many other medicines can interact. Sometimes serious side effects will happen if PREZISTA is taken with certain other medicines (see "Who should not take PREZISTA?").

Tell your doctor if you are taking estrogen-based contraceptives. PREZISTA might reduce the effectiveness of estrogen-based contraceptives. You must take additional precautions for birth control such as a condom.
Tell your doctor if you take other anti-HIV medicines. PREZISTA can be combined with some other anti-HIV medicines while other combinations are not recommended.

Tell your doctor if you are taking any of the following medicines:

** The brands listed are the registered trademarks of their respective owners and are not trademarks of Tibotec, Inc.

Type of Drug	Examples of Generic Names (Brand Names)
Antiarrhythmics (to treat abnormal heart rhythms)	bepridil (Vascor®) lidocaine (Lidoderm®) quinidine amiodarone (Cordarone®)
Anticoagulants (to prevent the clotting of red blood cells called platelets)	warfarin (Coumadin®)
Anticonvulsants (to treat epilepsy and prevent seizures)	carbamazepine (Tegretol®, Carbatrol®) phenobarbital phenytoin (Dilantin®, Phenytek®)
Antidepressants	trazodone (Desyrel®)
Anti-infectives (to treat bacterial infections)	clarithromycin (Biaxin®)
Antifungals (to treat fungal infections)	ketoconazole (Nizoral®) itraconazole (Sporanox®) voriconazole (Vfend®)
Antimycobacterials (to treat bacterial infections)	rifabutin (Mycobutin®) rifampin (Rifadin®, Rifater®, Rifamate®)
Calcium Channel Blockers (to treat heart disease)	felodipine (Plendil®) nifedipine (Adalat®) nicardipine (Cardene®)
Corticosteroids (to treat inflammation or asthma)	dexamethasone (Decadron®) fluticasone propionate (Advair Diskus®, Cutivate®, Flonase®, Flovent Diskus®)
HMG-CoA Reductase Inhibitors (to lower cholesterol levels)	atorvastatin (Lipitor®) lovastatin (Mevacor®) pravastatin (Pravachol®) simvastatin (Zocor®)
Immunosuppressants (to prevent organ transplant rejection)	cyclosporine (Sandimmune®, Neoral®) tacrolimus (Prograf®) sirolimus (Rapamune®)
Narcotic Analgesics	methadone
PDE-5 Inhibitors (to treat erectile dysfunction)	sildenafil (Viagra®) vardenafil (Levitra®)

Type of Drug	Examples of Generic Names (Brand Names)
	tadalafil (Cialis®)
Selective Serotonin Reuptake Inhibitors (SSRIs) (to treat depression, anxiety, or panic disorder)	paroxetine (Paxil®) sertraline (Zoloft®)

Tell your doctor if you are taking any medicines that you obtained without a prescription.

This is **not** a complete list of medicines that you should tell your doctor that you are taking. Know and keep track of all the medicines you take and have a list of them with you. Show this list to all of your doctors and pharmacists any time you get a new medicine. Both your doctor and your pharmacist can tell you if you can take these other medicines with PREZISTA. Do not start any new medicines while you are taking PREZISTA without first talking with your doctor or pharmacist. You can ask your doctor or pharmacist for a list of medicines that can interact with PREZISTA.

HOW SHOULD I TAKE PREZISTA?

Take PREZISTA tablets every day exactly as prescribed by your doctor. You must take ritonavir (NORVIR®) at the same time as PREZISTA. The usual dose is 600 mg (two 300 mg tablets) of PREZISTA, together with 100 mg (one 100 mg capsule) of ritonavir (NORVIR®), twice daily *every day.* It may be easier to remember to take PREZISTA and ritonavir (NORVIR®) if you take them at the same time every day. If you have questions about when to take PREZISTA and ritonavir (NORVIR®), your doctor can help you decide which schedule works for you.

Take PREZISTA and ritonavir (NORVIR®) **with food.** The type of food is not important. Swallow the whole tablets with a drink such as water or milk. Do not chew the tablets.

Continue taking PREZISTA and ritonavir (NORVIR®) unless your doctor tells you to stop. Take the exact amount of PREZISTA and ritonavir (NORVIR®) that your doctor tells you to take, right from the very start. To help make sure you will benefit from PREZISTA and ritonavir (NORVIR®), you must not skip doses or interrupt therapy. If you don't take PREZISTA and ritonavir (NORVIR®) as prescribed, the beneficial effects of PREZISTA and ritonavir (NORVIR®) may be reduced or even lost.

If you miss a dose of PREZISTA or ritonavir (NORVIR®) by more than 6 hours, wait and then take the next dose of PREZISTA and ritonavir (NORVIR®) at the regularly scheduled time. If you miss a dose of PREZISTA or ritonavir (NORVIR®) by less than 6 hours, take your missed dose of PREZISTA and ritonavir (NORVIR®) immediately. Then take your next dose of PREZISTA and ritonavir (NORVIR®) at the regularly scheduled time.

You should always take PREZISTA and ritonavir (NORVIR®) together with food.

If a dose of PREZISTA or ritonavir (NORVIR®) is skipped, do not double the next dose. Do not take more or less than your prescribed dose of PREZISTA or ritonavir (NORVIR®) at any one time.

WHAT ARE THE POSSIBLE SIDE EFFECTS OF PREZISTA?

Like all prescription drugs, PREZISTA can cause side effects. The following is **not** a complete list of side effects reported with PREZISTA when taken either alone or with other anti-HIV medicines. Do not rely on this leaflet alone for information about side effects. Your doctor can discuss with you a more complete list of side effects.

Mild to moderate rash has been reported in 7% of subjects receiving PREZISTA. In some patients, PREZISTA has been reported to cause a severe or life-threatening rash. Contact your healthcare provider if you develop a rash. Your healthcare provider will advise you whether your symptoms can be managed on therapy or whether PREZISTA should be stopped.

As with other protease inhibitors, PREZISTA may cause side effects, including:

- high blood sugar (hyperglycemia) and diabetes. This can happen in patients taking PREZISTA or other protease inhibitor medicines. Some patients have diabetes before starting treatment with PREZISTA which gets worse. Some patients get diabetes during treatment with PREZISTA. Some patients will need changes in their diabetes medicine. Some patients may need new diabetes medicine.
- increased bleeding in patients with hemophilia. This may happen in patients taking PREZISTA as it has been reported with other protease inhibitor medicines.
- changes in body fat. These changes can happen in patients taking anti-HIV medicines. The changes may include an increased amount of fat in the upper back and neck, breast, and around the back, chest, and stomach area. Loss of fat from the legs, arms, and face may also happen. The exact cause and long-term health effects of these conditions are not known.
- immune reconstitution syndrome. In some patients with advanced HIV infection (AIDS) and a history of opportunistic infection, signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms.

The most common side effects include diarrhea, nausea, headache, and common cold.

Tell your doctor promptly about these or any other unusual symptoms. If the condition persists or worsens, seek medical attention.

HOW SHOULD I STORE PREZISTA TABLETS?

Store PREZISTA tablets at room temperature (77°F (25°C)). Short-term exposure to higher or lower temperatures [from 59°F (15°C) to 86°F (30°C)] is acceptable. Ask your doctor or pharmacist if you have any questions about storing your tablets.

This medication is prescribed for your particular condition. Do not use it for any other condition or give it to anybody else. Keep PREZISTA and all of your medicines out of the reach of children. If you suspect that more than the prescribed dose of this medicine has been taken, contact your local poison control center or emergency room immediately.

This leaflet provides a summary of information about PREZISTA. If you have any questions or concerns about either PREZISTA or HIV, talk to your doctor.

For additional information, you may also call Tibotec Therapeutics at 1-800-325-7504.

Rx Only

Manufactured for Tibotec, Inc. by:
JOLLC, Gurabo, Puerto Rico
Distributed by:
Tibotec Therapeutics, Division of Ortho Biotech Products, L.P., Raritan NJ 08869

Issued: June 2006

10101700

Exhibit 3

Copy of U.S. Patent No. 6,248,775

US006248775B1

(12) **United States Patent**
Vazquez et al.

(10) **Patent No.: US 6,248,775 B1**
(45) **Date of Patent: Jun. 19, 2001**

(54) **α- AND β-AMINO ACID HYDROXYETHYLAMINO SULFONAMIDES USEFUL AS RETROVIRAL PROTEASE INHIBITORS**

(75) Inventors: **Michael L. Vazquez**, Gurnee; **Richard A. Mueller**, Glencoe, both of IL (US); **John J. Talley**, Brentwood, MO (US); **Daniel P. Getman**, Chestertfield, MO (US); **Gary A. DeCrescenzo**, St. Peters, MO (US); **John N. Freskos**, Clayton, MO (US); **Deborah E. Bertenshaw**, Brentwood, MO (US); **Robert M. Heintz**, Ballwin, MO (US)

(73) Assignee: **G. D. Searle & Co.**, Chicago, IL (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/288,080**

(22) Filed: **Apr. 8, 1999**

Related U.S. Application Data

(63) Continuation of application No. 08/294,468, filed on Aug. 24, 1994, now Pat. No. 5,968,942, which is a continuation-in-part of application No. 08/204,827, filed on Mar. 2, 1994, now Pat. No. 6,060,476, which is a continuation-in-part of application No. PCT/US93/07814, filed on Aug. 24, 1993, and a continuation-in-part of application No. 08/110,911, filed on Aug. 24, 1993, now Pat. No. 5,843,946, which is a continuation-in-part of application No. 07/934,984, filed on Aug. 25, 1992, now abandoned.

(51) **Int. Cl.**[7] **A61K 31/38**; A61K 31/34; C07D 333/32; C07D 307/93

(52) **U.S. Cl.** **514/445**; 514/470; 549/65; 549/465

(58) **Field of Search** 514/445, 470; 549/65, 465

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Primary Examiner—Deborah C. Lambkin
(74) *Attorney, Agent, or Firm*—Banner & Witcoff, Ltd.

(57) **ABSTRACT**

α- and β-amino acid hydroxyethylamino sulfonamide compounds are effective as retroviral protease inhibitors, and in particular as inhibitors of HIV protease.

18 Claims, No Drawings

α- AND β-AMINO ACID HYDROXYETHYLAMINO SULFONAMIDES USEFUL AS RETROVIRAL PROTEASE INHIBITORS

RELATED APPLICATION

This application is a continuation of Ser. No. 08/294,468 filed Aug. 24, 1994, U.S. Pat. No. 5,968,942, which is a continuation in part application of U.S. patent application Ser. No. 08/204,827 filed Mar. 2, 1994 now U.S. Pat. No. 6,060,476, which is a continuation in part application of PCT/US93/07814, and Ser. No. 08/110,911 (now U.S. Pat. No. 5,843,946) both, filed Aug. 24, 1993, which is a continuation in part application of co-owned U.S. patent application Ser. No. 07/934,984 filed Aug. 25, 1992, now abandoned, each of which is incorporated herein by reference in its entirety.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to retroviral protease inhibitors and, more particularly, relates to novel compounds and a composition and method for inhibiting retroviral proteases. This invention, in particular, relates to sulfonamide-containing hydroxyethylamine protease inhibitor compounds, a composition and method for inhibiting retroviral proteases such as human immunodeficiency virus (HIV) protease and for treating a retroviral infection, e.g., an HIV infection. The subject invention also relates to processes for making such compounds as well as to intermediates useful in such processes.

2. Related Art

During the replication cycle of retroviruses, gag and gag-pol gene transcription products are translated as proteins. These proteins are subsequently processed by a virally encoded protease (or proteinase) to yield viral enzymes and structural proteins of the virus core. Most commonly, the gag precursor proteins are processed into the core proteins and the pol precursor proteins are processed into the viral enzymes, e.g., reverse transcriptase and retroviral protease. It has been shown that correct processing of the precursor proteins by the retroviral protease is necessary for assembly of infectious virons. For example, it has been shown that frameshift mutations in the protease region of the pol gene of HIV prevents processing of the gag precursor protein. It has also been shown through site-directed mutagenesis of an aspartic acid residue in the HIV protease active site that processing of the gag precursor protein is prevented. Thus, attempts have been made to inhibit viral replication by inhibiting the action of retroviral proteases.

Retroviral protease inhibition typically involves a transition-state mimetic whereby the retroviral protease is exposed to a mimetic compound which binds (typically in a reversible manner) to the enzyme in competition with the gag and gag-pol proteins to thereby inhibit specific processing of structural proteins and the release of retroviral protease itself. In this manner, retroviral replication proteases can be effectively inhibited.

Several classes of compounds have been proposed, particularly for inhibition of proteases, such as for inhibition of HIV protease. Such compounds include hydroxyethylamine isosteres and reduced amide isosteres. See, for example, EP O 346 847; EP O 342,541; Roberts et al, "Rational Design of Peptide-Based Proteinase Inhibitors, "Science, 248, 358 (1990); and Erickson et al, "Design Activity, and 2.8 Å Crystal Structure of a C_2 Symmetric Inhibitor Complexed to HIV-1 Protease," Science, 249, 527 (1990).

Several classes of compounds are known to be useful as inhibitors of the proteolytic enzyme renin. See, for example, U.S. Pat. No. 4,599,198; U.K. 2,184,730; G.B. 2,209,752; EP O 264 795; G.B. 2,200,115 and U.S. SIR H725. Of these, G.B. 2,200,115, GB 2,209,752, EP O 264,795, U.S. SIR H725 and U.S. Pat. No. 4,599,198 disclose urea-containing hydroxyethylamine renin inhibitors. EP 468 641 discloses renin inhibitors and intermediates for the preparation of the inhibitors, which include sulfonamide-containing hydroxyethylamine compounds, such as 3-(t-butoxycarbonyl)amino-cyclohexyl-1-(phenylsulfonyl)amino-2(5)-butanol. G.B. 2,200,115 also discloses sulfamoyl-containing hydroxyethylamine renin inhibitors, and EP 0264 795 discloses certain sulfonamide-containing hydroxyethylamine renin inhibitors. However, it is known that, although renin and HIV proteases are both classified as aspartyl proteases, compounds which are effective renin inhibitors generally cannot be predicted to be effective HIV protease inhibitors.

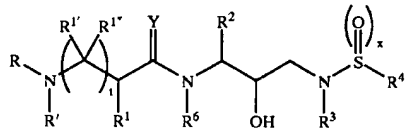
BRIEF DESCRIPTION OF THE INVENTION

The present invention is directed to virus inhibiting compounds and compositions. More particularly, the present invention is directed to retroviral protease inhibiting compounds and compositions, to a method of inhibiting retroviral proteases, to processes for preparing the compounds and to intermediates useful in such processes. The subject compounds are characterized as sulfonamide-containing hydroxyethylamine inhibitor compounds.

DETAILED DESCRIPTION OF THE INVENTION

In accordance with the present invention, there is provided a retroviral protease inhibiting compound of the formula:

(I)



or a pharmaceutically acceptable salt, prodrug or ester thereof, wherein:

R represents hydrogen, alkoxycarbonyl, aralkoxycarbonyl, alkylcarbonyl, cycloalkylcarbonyl, cycloalkylalkoxycarbonyl, cycloalkylalkanoyl, alkanoyl, aralkanoyl, aroyl, aryloxycarbonyl, aryloxycarbonylalkyl, aryloxyalkanoyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, heterocyclylalkanoyl, heterocyclylalkoxycarbonyl, heteroaralkanoyl, heteroaralkoxycarbonyl, heteroaryloxycarbonyl, heteroaroyl, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, aryloxyalkyl, heteroaryloxyalkyl, hydroxyalkyl, aminocarbonyl, aminoalkanoyl, and mono- and disubstituted aminocarbonyl and mono- and disubstituted aminoalkanoyl radicals wherein the substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, heterocycloalkyalkyl radicals, or where said aminocarbonyl and aminoalkanoyl radicals are disubstituted, said substituents along with the nitrogen atom to which they are attached form a heterocycloalkyl or heteroaryl radical;

R' represents hydrogen, radicals as defined for R^3 or R"SO_2— wherein R" represents radicals as defined for R^3;

or R and R' together with the nitrogen to which they are attached represent heterocycloalkyl and heteroaryl radicals;

R^1 represents hydrogen, —$CH_2SO_2NH_2$, —$CH_2CO_2CH_3$, —CO_2CH_3, —$CONH_2$, —$CH_2C(O)NHCH_3$, —$C(CH_3)_2(SH)$, —$C(CH_3)_2(SCH_3)$, —$C(CH_3)_2(S[O]CH_3)$, —$C(CH_3)_2(S[O]_2CH_3)$, alkyl, haloalkyl, alkenyl, alkynyl and cycloalkyl radicals, and amino acid side chains selected from asparagine, S-methyl cysteine and the sulfoxide (SO) and sulfone (SO_2) derivatives thereof, isoleucine, allo-isoleucine, alanine, leucine, tert-leucine, phenylalanine, ornithine, histidine, norleucine, glutamine, threonine, allo-threonine, serine, O-alkyl serine, aspartic acid, beta-cyano alanine and valine side chains;

$R^{1'}$ and $R^{1''}$ independently represent hydrogen and radicals as defined for R^1, or one of $R^{1'}$ and $R^{1''}$, together with R^1 and the carbon atoms to which R^1, $R^{1'}$ and $R^{1''}$ are attached, represent a cycloalkyl radical;

R^2 represents alkyl, aryl, cycloalkyl, cycloalkylalkyl and aralkyl radicals, which radicals are optionally substituted with a group selected from alkyl and halogen radials, —NO_2, —CN, —CF_3, —OR^9 and —SR^9, wherein R^9 represents hydrogen and alkyl radicals, and halogen radicals;

R^3 represents hydrogen, alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, beteroaryl, heterocycloalkylalkyl, aryl, aralkyl, heteroaralkyl, aminoalkyl and mono- and disubstituted aminoalkyl radicals, wherein said substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, and heterocycloalkylalkyl radicals, or in the case of a disubstituted aminoalkyl radical, said substituents along with the nitrogen atom to which they are attached, form a heterocycloalkyl or a heteroaryl radical;

R^4 represents radicals as defined by R^3 except for hydrogen;

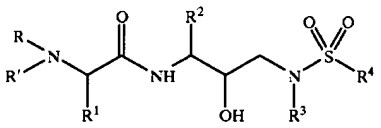
R^6 represents hydrogen and alkyl radicals;

x represents 0, 1 or 2;

t represents either 0 or 1; and

Y represents O, S and NR^{15} wherein R^{15} represents hydrogen and radicals as defined for R^3.

A family of compounds of particular interest within Formula I are compounds embraced by Formula II:



(II)

wherein:

R represents hydrogen, alkoxycarbonyl, aralkoxycarbonyl, alkylcarbonyl, cycloalkylcarbonyl, cycloalkylalkoxycarbonyl, cycloalkylalkanoyl, alkanoyl, aralkanoyl, aroyl, aryloxycarbonyl, aryloxycarbonylalkyl, aryloxyalkanoyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, heterocyclylalkanoyl, heterocyclylalkoxycarbonyl, heteroaralkanoyl, heteroaralkoxycarbonyl, heteroaryloxy-carbonyl, heteroaroyl, alkyl, alkenyl, cycloalkyl, aryl, aralkyl, aryloxyalkyl, heteroaryloxyalkyl, hydroxyalkyl, aminocarbonyl, aminoalkanoyl, and mono- and disubstituted aminocarbonyl and mono- and disubstituted aminoalkanoyl radicals wherein the substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, heterocycloalkylalkyl radicals, or where said aminoalkanoyl radical is disubstituted, said substituents along with the nitrogen atom to which they are attached form a heterocycloalkyl or heteroaryl radical;

R' represents hydrogen and radicals as defined for R^3 or R and R' together with the nitrogen to which they are attached represent heterocycloalkyl and heteroaryl radical;

R^1 represents hydrogen, —$CH_2SO_2NH_2$, —$CH_2CO_2CH_3$, —CO_2CH_3, —$CONH_2$, —$CH_2C(O)NHCH_3$, —$C(CH_3)_2(SH)$, —$C(CH_3)_2(SCH_3)$, —$C(CH_3)_2(S[O]CH_3)$, —$C(CH_3)_2(S[O]_2CH_3)$, alkyl, haloalkyl, alkenyl, alkynyl and cycloalkyl radicals, and amino acid side chains selected from asparagine, S-methyl cysteine and the sulfoxide (SO) and sulfone (SO_2) derivatives thereof, isoleucine, allo-isoleucine, alanine, leucine, tert-leucine, phenylalanine, ornithine, histidine, norleucine, glutamine, threonine, allo-threonine, serine, O-methyl serine, aspartic acid, beta-cyano alanine and valine side chains;

R^2 represents alkyl, aryl, cycloalkyl, cycloalkylalkyl and aralkyl radicals, which radicals are optionally substituted with a group selected from alkyl and halogen radials, —NO_2, —C≡N, CF_3, —OR^9, —SR^9, wherein R^9 represents hydrogen and alkyl radicals;

R^3 represents alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heteroaryl, heterocycloalkylalkyl, aryl, aralkyl, heteroaralkyl, aminoalkyl and mono- and disubstituted aminoalkyl radicals, wherein said substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, and heterocycloalkylalkyl radicals, or in the case of a disubstituted aminoalkyl radical, said substituents along with the nitrogen atom to which they are attached, form a heterocycloalkyl or a heteroaryl radical; and

R^4 represents radicals as defined by R^3.

A more preferred family of compounds within Formula II consists of compounds wherein:

R represents hydrogen, alkoxycarbonyl, aralkoxycarbonyl, alkylcarbonyl, cycloalkylcarbonyl, cycloalkylalkoxycarbonyl, cycloalkylalkanoyl, alkanoyl, aralkanoyl, aroyl, aryloxycarbonyl, aryloxycarbonylalkyl, aryloxyalkanoyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, heterocyclylalkanoyl, heterocyclylalkoxycarbonyl, heteroaralkanoyl, heteroaralkoxycarbonyl, heteroaryloxy-carbonyl, heteroaroyl, alkyl, alkenyl, cycloalkyl, aryl, aralkyl, aryloxyalkyl, heteroaryloxyalkyl, hydroxyalkyl, aminocarbonyl, aminoalkanoyl, and mono- and disubstituted aminocarbonyl and mono- and disubstituted aminoalkanoyl radicals wherein the substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, heterocycloalkylalkyl radicals, or where said aminoalkanoyl radical is disubstituted, said substituents along with the nitrogen atom to which they are attached form a heterocycloalkyl or heteroaryl radical;

R' represents hydrogen and radicals as defined for R^3 or R and R' together with the nitrogen to which they are attached represent heterocycloalkyl and heteroaryl radical;

R^1 represents $CH_2C(O)NHCH_3$, $C(CH_3)_2(SCH_3)$, $C(CH_3)_2(S[O]CH_3)$, $C(CH_3)_2(S[O]_2CH_3)$, alkyl, alkenyl and alky-

nyl radicals, and amino acid side chains selected from the group consisting of asparagine, valine, threonine, allo-threonine, isoleucine, tert-leucine, S-methyl cysteine and the sulfone and sulfoxide derivatives thereof, alanine, and allo-isoleucine;

R^2 represents alkyl, cycloalkylalkyl and aralkyl radicals, which radicals are optionally substituted with halogen radicals and radicals represented by the formula —OR^9 and —SR^9 wherein R^9 represents alkyl radicals; and

R^3 and R^4 independently represent alkyl, alkenyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, aralkyl and heteroaralkyl radicals.

Of highest interest are compounds within Formula II wherein

R represents alkoxycarbonyl, aralkoxycarbonyl, alkylcarbonyl, cycloalkylcarbonyl, cycloalkylalkoxycarbonyl, cycloalkylalkanoyl, alkanoyl, aralkanoyl, aroyl, aryloxycarbonyl, aryloxycarbonylalkyl, aryloxyalkanoyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, heterocyclylalkanoyl, heterocyclylalkoxycarbonyl, heteroaralkanoyl, heteroaralkoxycarbonyl, heteroaryloxy-carbonyl, heteroaroyl, aminocarbonyl, aminoalkanoyl, and mono- and disubstituted aminocarbonyl and mono- and disubstituted aminoalkanoyl radicals wherein the substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, heterocycloalkyalkyl radicals, or where said aminoalkanoyl radical is disubstituted, said substituents along with the nitrogen atom to which they are attached form a heterocycloalkyl or heteroaryl radical;

R' represents hydrogen and radicals as defined for R^3 or R and R' together with the nitrogen to which they are attached represent heterocycloalkyl and heteroaryl radical;

R^1 represents $CH_2C(O)NHCH_3$, $C(CH_3)_2(SCH_3)$, $C(CH_3)_2(S[O]CH_3)$, $C(CH_3)_2(S[O]_2CH_3)$, methyl, propargyl, t-butyl, isopropyl and sec-butyl radicals, and amino acid side chains selected from the group consisting of asparagine, valine, S-methyl cysteine, allo-iso-leucine, iso-leucine, and beta-cyano alanine side chains;

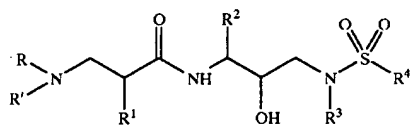
R^2 represents $CH_3SCH_2CH_2$—, iso-butyl, n-butyl, benzyl, 4-fluorobenzyl, 2-naphthylmethyl and cyclohexylmethyl radicals;

R^3 represents isoamyl, n-butyl, isobutyl and cyclohexyl radicals; and

R^4 represents phenyl, substituted phenyl and methyl radicals.

Another family of compounds of particular interest within Formula I are compounds embraced by Formula III:

(III)



wherein:

R represents hydrogen, alkoxycarbonyl, aralkoxycarbonyl, alkylcarbonyl, cycloalkylcarbonyl, cycloalkylalkoxycarbonyl, cycloalkylalkanoyl, alkanoyl, aralkanoyl, aroyl, aryloxycarbonyl, aryloxycarbonylalkyl, aryloxyalkanoyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, heterocyclylalkanoyl, heterocyclylalkoxycarbonyl, heteroaralkanoyl, heteroaralkoxycarbonyl, heteroaryloxy-carbonyl, heteroaroyl, alkyl, alkenyl, cycloalkyl, aryl, aralkyl, aryloxyalkyl, heteroaryloxyalkyl, hydroxyalkyl, aminocarbonyl, aminoalkanoyl, and mono- and disubstituted aminocarbonyl and mono- and disubstituted aminoalkanoyl radicals wherein the substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, heterocycloalkyalkyl radicals, or where said aminoalkanoyl radical is disubstituted, said substituents along with the nitrogen atom to which they are attached form a heterocycloalkyl or heteroaryl radical;

R' represents hydrogen and radicals as defined for R^3 or R and R' together with the nitrogen to which they are attached represent heterocycloalkyl and heteroaryl radical;

R^1 represents hydrogen, $—CH_2SO_2NH_2$, $—CH_2CO_2CH_3$, $—CO_2CH_3$, $—CONH_2$, $—CH_2C(O)NHCH_3$, $—C(CH_3)_2(SH)$, $—C(CH_3)_2(SCH_3)$, $—C(CH_3)_2(S[O]CH_3)$, $—C(CH_3)_2(S[O]_2CH_3)$, alkyl, haloalkyl, alkenyl, alkynyl and cycloalkyl radicals, and amino acid side chains selected from asparagine, S-methyl cysteine and the sulfoxide (SO) and sulfone (SO_2) derivatives thereof, isoleucine, allo-isoleucine, alanine, leucine, tert-leucine, phenylalanine, ornithine, histidine, norleucine, glutamine, threonine, allo-threonine, serine, aspartic acid, beta-cyano alanine and valine side chains;

R^2 represents alkyl, aryl, cycloalkyl, cycloalkylalkyl and aralkyl radicals, which radicals are optionally substituted with a group selected from alkyl and halogen radicals, $—NO_2$, —C≡N, CF_3, $—OR^9$, $—SR^9$, wherein R^9 represents hydrogen and alkyl;

R^3 represents alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heteroaryl, heterocycloalkylalkyl, aryl, aralkyl, heteroaralkyl, aminoalkyl and mono- and disubstituted aminoalkyl radicals, wherein said substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, and heterocycloalkylalkyl radicals, or in the case of a disubstituted aminoalkyl radical, said substituents along with the nitrogen atom to which they are attached, form a heterocycloalkyl or a heteroaryl radical; and

R^4 represents radicals as defined by R^3.

A more preferred family of compounds within Formula III consists of compounds wherein

R represents hydrogen, alkoxycarbonyl, aralkoxycarbonyl, alkylcarbonyl, cycloalkylcarbonyl, cycloalkylalkoxycarbonyl, cycloalkylalkanoyl, alkanoyl, aralkanoyl, aroyl, aryloxycarbonyl, aryloxycarbonylalkyl, aryloxyalkanoyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, heterocyclylalkanoyl, heterocyclylalkoxycarbonyl, heteroaralkanoyl, heteroaralkoxycarbonyl, heteroaryloxy-carbonyl, heteroaroyl, alkyl, alkenyl, cycloalkyl, aryl, aralkyl, aryloxyalkyl, heteroaryloxyalkyl, hydroxyalkyl, aminocarbonyl, aminoalkanoyl, and mono- and disubstituted aminocarbonyl and mono- and disubstituted aminoalkanoyl radicals wherein the substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, heterocycloalkyalkyl radicals, or where said aminoalkanoyl radical is disubstituted, said substituents along with the nitrogen atom to which they are attached form a heterocycloalkyl or heteroaryl radical;

R' represents hydrogen and radicals as defined for R^3 or R and R' together with the nitrogen to which they are attached represent heterocycloalkyl and heteroaryl radical;

R^1 represents hydrogen, alkyl and alkenyl radicals, and amino acid side chains selected from the group consisting of asparagine, valine, threonine, allo-threonine, isoleucine, tert-leucine, S-methyl cysteine and the sulfone and sulfoxide derivatives thereof, alanine, and allo-isoleucine;

R^2 represents alkyl, cycloalkylalkyl and aralkyl radicals, which radicals are optionally substituted with halogen radicals and radicals represented by the formula —OR^9 and —SR^9 wherein R^9 represents hydrogen and alkyl and halogen radicals; and

R^3 and R^4 independently represent alkyl, alkenyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, aralkyl, heteroaryl and heteroaralkyl radicals.

Of highest interest are compounds within Formula III wherein

R represents hydrogen, alkoxycarbonyl, aralkoxycarbonyl, alkylcarbonyl, cycloalkylcarbonyl, cycloalkylalkoxycarbonyl, cycloalkylalkanoyl, alkanoyl, aralkanoyl, aroyl, aryloxycarbonyl, aryloxycarbonylalkyl, aryloxyalkanoyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, heterocyclylalkanoyl, heterocyclylalkoxycarbonyl, heteroaralkanoyl, heteroaralkoxycarbonyl, heteroaryloxy-carbonyl, heteroaroyl, aminocarbonyl, aminoalkanoyl, and mono- and disubstituted aminocarbonyl and mono- and disubstituted aminoalkanoyl radicals wherein the substituents. are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, heterocycloalkyalkyl radicals, or where said aminoalkanoyl radical is disubstituted, said substituents along with the nitrogen atom to which they are attached form a heterocycloalkyl or heteroaryl radical;

R' represents hydrogen and radicals as defined for R^3 or R and R' together with the nitrogen to which they are attached represent heterocycloalkyl and heteroaryl radical;

R^1 represents hydrogen, methyl, propargyl, t-butyl, isopropyl and sec-butyl radicals, and amino acid side chains selected from the group consisting of asparagine, valine, S-methyl cysteine, allo-iso-leucine, iso-leucine, threonine, serine, aspartic acid, beta-cyano alanine, and allo-threonine side chains;

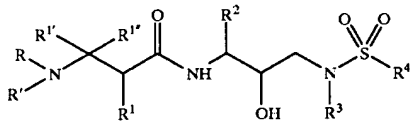
R^2 represents $CH_3SCH_2CH_2$—, iso-butyl, n-butyl, benzyl, 4-fluorobenzyl, 2-naphthylmethyl and cyclohexylmethyl radicals; and

R^3 represents alkyl, cyclohexyl, isobutyl, isoamyl, and n-butyl radicals; and

R^4 represents methyl, phenyl and substituted phenyl radicals wherein the substituents are selected from halo, alkoxy, hydroxy, nitro and amino substituents.

Another family of compounds of particular interest within Formula I are compounds embraced by Formula IV:

(IV)



wherein:

R represents hydrogen, alkoxycarbonyl, aralkoxycarbonyl, alkylcarbonyl, cycloalkylcarbonyl; cycloalkylalkoxycarbonyl, cycloalkylalkanoyl, alkanoyl, aralkanoyl, aroyl, aryloxycarbonyl, aryloxycarbonylalkyl, aryloxyalkanoyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, heterocyclylalkanoyl, heterocyclylalkoxycarbonyl, heteroaralkanoyl, heteroaralkoxycarbonyl, heteroaryloxy-carbonyl, heteroaroyl, alkyl, alkenyl, cycloalkyl, aryl, aralkyl, aryloxyalkyl, heteroaryloxyalkyl, hydroxyalkyl, aminocarbonyl, aminoalkanoyl, and mono- and disubstituted aminocarbonyl and mono- and disubstituted aminoalkanoyl radicals wherein the substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, heterocycloalkyalkyl radicals, or where said aminoalkanoyl radical is disubstituted, said substituents along with the nitrogen atom to which they are attached form a heterocycloalkyl or heteroaryl radical;

R' represents hydrogen and radicals as defined for R^3 or R and R' together with the nitrogen to which they are attached represent heterocycloalkyl and heteroaryl radical;

R^1 represents hydrogen, —$CH_2SO_2NH_2$, —$CH_2CO_2CH_3$, —CO_2CH_3, —$CONH_2$, —$CH_2C(O)NHCH_3$, —$C(CH_3)_2(SH)$, —$C(CH_3)_2(SCH_3)$, —$C(CH_3)_2(S[O]CH_3)$, —$C(CH_3)_2(S[O]_2CH_3)$, alkyl, haloalkyl, alkenyl, alkynyl and cycloalkyl radicals, and amino acid side chains selected from asparagine, S-methyl cysteine and the sulfoxide (SO) and sulfone (SO_2) derivatives thereof, isoleucine, allo-isoleucine, alanine, leucine, tert-leucine, phenylalanine, ornithine, histidine, norleucine, glutamine, threonine, allo-threonine, serine, aspartic acid, beta-cyano alanine and valine side chains;

$R^{1'}$ and $R^{1''}$ independently represent hydrogen and radicals as defined for R^1, or one of $R^{1'}$ and $R^{1''}$, together with R^1 and the carbon atoms to which R^1, $R^{1'}$ and $R^{1''}$ are attached, represent a cycloalkyl radical;

R^2 represents alkyl, aryl, cycloalkyl, cycloalkylalkyl and aralkyl radicals, which radicals are optionally substituted with a group selected from alkyl and halogen radials, —NO_2, —C≡N, CF_3, —OR^9 and —SR^9, wherein R^9 represents hydrogen and alkyl radicals;

R^3 represents alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heteroaryl, heterocycloalkylalkyl, aryl, aralkyl, heteroaralkyl, aminoalkyl and mono- and disubstituted aminoalkyl radicals, wherein said substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, and heterocycloalkylalkyl radicals, or in the case of a disubstituted aminoalkyl radical, said substituents along with the nitrogen atom to which they are attached, form a heterocycloalkyl or a heteroaryl radical; and

R^4 represents radicals as defined by R^3.

A more preferred family of compounds within Formula IV consists of compounds wherein

R represents an arylalkanoyl, heteroaroyl, aryloxyalkanoyl, aryloxycarbonyl, alkanoyl, aminocarbonyl, monosubstituted aminoalkanoyl, or disubstituted aminoalkanoyl, or mono- or dialkylaminocarbonyl radical;

R' represents hydrogen and radicals as defined for R^3 or R and R' together with the nitrogen to which they are attached represent a heterocycloalkyl or heteroaryl radical;

R^1, $R^{1'}$ and $R^{1''}$ independently represent hydrogen and alkyl radicals having from 1 to about 4 carbon atoms, alkenyl, alkynyl, aralkyl radicals, and radicals represented by the formula —$CH_2C(O)R''$ or —$C(O)R''$ wherein R'' repre-

sents R^{38}, —$NR^{38}R^{39}$ and OR^{38} wherein R^{38} and R^{39} independently represent hydrogen and alkyl radicals having from 1 to about 4 carbon atoms;

R^2 represents alkyl, cycloalkylalkyl and aralkyl radicals, which radicals are optionally substituted with halogen radicals and radicals represented by the formula —OR^9 and —SR^9 wherein R^9 represents hydrogen and alkyl radicals; and

R^3 and R^4 independently represent alkyl, alkenyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, aralkyl, heteroaryl and heteroaralkyl radicals.

Of highest interest are compounds of Formula IV wherein:

R represents an arylalkanoyl, aryloxycarbonyl, aryloxyalkanoyl, alkanoyl, aminocarbonyl, monosubstituted aminoalkanoyl, or disubstituted aminoalkanoyl, or mono -or dialkylaminocarbonyl radical;

R' represents hydrogen and radicals as defined for R^3 or R and R' together with the nitrogen to which they are attached represent a heterocycloalkyl or heteroaryl radical;

R^1, $R^{1'}$ and $R^{1''}$ independently represent hydrogen, methyl, ethyl, benzyl, phenylpropyl and propargyl radicals;

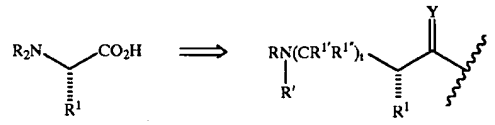
R^2 represents $CH_3SCH_2CH_2$—, iso-butyl, n-butyl, benzyl, 4-fluorobenzyl, 2-naphthylmethyl and cyclohexylmethyl radicals;

R^3 represents alkyl, cyclobexyl, isobutyl, isoamyl and n-butyl radicals; and

R^4 represents methyl, phenyl and substituted phenyl radicals wherein the substituents are selected from halo, alkoxy, amino and nitro substituents.

As utilized herein, the term "alkyl", alone or in combination, means a straight-chain or branched-chain alkyl radical containing from 1 to about 10 carbon atoms, preferably from 1 to about 8 carbon atoms, more preferably 1–5 carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl, octyl and the like. The term "alkenyl", alone or in combination, means a straight-chain or branched-chain hydrocarbon radial having one or more double bonds and containing from 2 to about 18 carbon atoms, preferably from 2 to about 8 carbon atoms, more preferably from 2 to about 5 carbon atoms. Examples of suitable alkenyl radicals include ethenyl, propenyl, alkyl, 1,4-butadienyl and the like. The term "alkynyl", alone or in combination, means a straight-chain or branched chain hydrocarbon radical having one or more triple bonds and containing from 2 to about 10 carbon atoms, more preferably from 2 to about 5 carbon atoms. Examples of alkynyl radicals include ethynyl, propynyl, (propargyl), butynyl and the like. The term "alkoxy", alone or in combination, means an alkyl ether radical wherein the term alkyl is as defined above. Examples of suitable alkyl ether radicals include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy and the like. The term "cycloalkyl", alone or in combination, means a saturated or partially saturated monocyclic, bicyclic or tricyclic alkyl radical wherein each cyclic moiety contains from about 3 to about 8 carbon atoms, more preferably from about 3 to about 6 carbon atoms. Examples of such cycloalkyl radicals include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like. The term "cycloalkylalkyl" means an alkyl radical as defined above which is substituted by a cycloalkyl radical as defined above. Examples of such cycloalkylalkyl radicals include cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, 1-cyclopentylethyl, 1-cyclohexylethyl, 2-cyclopentylethyl, 2-cyclohexylethyl, cyclobutylpropyl, cyclopentylpropyl, cyclohexylbutyl and the like. The term "aryl", alone or in combination, means a phenyl or naphthyl radical which optionally carries one or more substituents selected from alkyl, alkoxy, halogen, hydroxy, amino, nitro, cyano, haloalkyl, carboxy, alkoxycarbonyl, cycloalkyl, heterocycloalkyl, amido, mono and dialkyl substituted amino, mono and dialkyl substituted amido and the like, such as phenyl, p-tolyl, 4-methoxyphenyl, 4-(tert-butoxy)phenyl, 3-methyl-4-methoxyphenyl, 4-fluorophenyl, 4-chlorophenyl, 3-nitrophenyl, 3-aminophenyl, 3-acetamidophenyl, 4-acetamidophenyl, 2-methyl-3-acetamidophenyl, 2-methyl-3-aminophenyl, 3-methyl-4-aminophenyl, 2-amino-3-methylphenyl, 2,4-dimethyl-3-aminophenyl, 4-hydroxyphenyl, 3-methyl-4-hydroxyphenyl, 1-naphthyl, 2-naphthyl, 3-amino-1-naphthyl, 2-methyl-3-amino-1-naphthyl, 6-amino-2-naphthyl, 4,6-dimethoxy-2-naphthyl and the like. The terms "aralkyl" and "aralkoxy", alone or in combination, means an alkyl or alkoxy radical as defined above in which at least one hydrogen atom is replaced by an aryl radical as defined above, such as benzyl, benzyloxy, 2-phenylethyl, dibenzylmethyl, hydroxyphenylmethyl, methylphenylmethyl, and the like. The term "aralkoxycarbonyl", alone or in combination, means a radical of the formula aralkyl-O—C(O)— in which the term "aralkyl" has the significance given above. Examples of an aralkoxycarbonyl radical are benzyloxycarbonyl and 4-methoxyphenylmethoxycarbonyl. The term "aryloxy" means a radical of the formula aryl-O— in which the term aryl has the significance given above. The term "alkanoyl", alone or in combination, means an acyl radical derived from an alkanecarboxylic acid, examples of which include acetyl, propionyl, butyryl, valeryl, 4-methylvaleryl, and the like. The term "cycloalkylcarbonyl" means an acyl group derived from a monocyclic or bridged cycloalkanecarboxylic acid such as cyclopropylcarbonyl, cyclohexylcarbonyl, adamantylcarbonyl, and the like, or from a benz-fused monocyclic cycloalkanecarboxylic acid which is optionally substituted by one or more substituents selected from alkyl, alkoxy, halogen, hydroxy, amino, nitro, cyano, haloalkyl, carboxy, alkoxycarbonyl, cycloalkyl, heterocycloalkyl, alkanoylamino, amido, mono and dialkyl substituted amino, mono and dialkyl substituted amido and the like, such as 1,2,3,4-tetrahydro-2-naphthoyl, 2-acetamido-1,2,3,4-tetrahydro-2-naphthoyl. The term "aralkanoyl" means an acyl radical derived from an aryl-substituted alkanecarboxylic acid such as phenylacetyl, 3-phenylpropionyl (hydrocinnamoyl), 4-phenylbutyryl, (2-naphthyl)acetyl, 4-chlorohydrocinnamoyl, 4-aminohydrocinnamoyl,4-methoxyhydrocinnamoyl, and the like. The term "aroyl", means an acyl radical derived from an arylcarboxylic acid, aryl having the meaning given above. Examples of such arylcarboxylic acid radicals include substituted and unsubstituted benzoic or naphthoic acid such as benzoyl, 4-chlorobenzoyl, 4-carboxybenzoyl, 4-(benzyloxycarbonyl) benzoyl, 1-naphthoyl, 2-naphthoyl, 6-carboxy-2 naphthoyl, 6-(benzyloxycarbonyl)-2-naphthoyl, 3-benzyloxy-2-naphthoyl, 3-hydroxy-2-naphthoyl, 3-(benzyloxyformamido)-2-naphthoyl, and the like. The terms "heterocyclyl" and "heterocycloalkyl," alone or in combination, mean a saturated or partially unsaturated monocyclic, bicyclic or tricyclic heterocycle having preferably 3 to 12 ring members, more preferably 5 to 10 ring members and most preferably 5 to 6 ring members, which contains one or more heteroatom ring members selected

from nitrogen, oxygen and sulphur, and which is optionally substituted on one or more carbon atoms by halogen, alkyl, alkoxy, hydroxy, oxo, aryl, aralkyl and the like, and/or on a secondary nitrogen atom (i.e., —NH—) by hydroxy, alkyl, aralkoxycarbonyl, alkanoyl, phenyl or phenylalkyl and/or on a tertiary nitrogen atom (i.e., =N—) by oxido. Heterocycloalkyl and heterocyclyl also includes benz-fused monocyclic cycloalkyl groups having at least one such heteroatom. Heterocycloalkyl and heterocyclyl in addition to sulfur and nitrogen also includes sulfones, sulfoxides and N-oxides of tertiary nitrogen containing heterocycloalkyl groups. The term "heteroaryl", alone or in combination, means an aromatic monocyclic, bicyclic, or tricyclic heterocyclyl (heterocycloalkyl) radical as defined above and is optionally substituted as defined above with respect to the definitions of aryl and heterocyclyl (heterocycloalkyl). Examples of such heterocyclyl (heterocycloalkyl) and heteroaryl groups are pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiamorpholinyl, pyrrolyl, imidazolyl (e.g., imidazol 4-yl, 1-benzyloxycarbonylimidazol-4-yl, etc.), pyrazolyl, pyridyl, (e.g., 2-(1-piperidinyl)pyridyl and 2-(4-benzyl piperazin-1-yl-1-pyridinyl), pyrazinyl, pyrimidinyl, furyl, tetrahydrofuryl, thienyl, triazolyl, oxazolyl, thiazolyl, indolyl (e.g., 2-indolyl, etc.), quinolinyl, (e.g., 2-quinolinyl, 3-quinolinyl, 1-oxido-2-quinolinyl, etc.), isoquinolinyl (e.g., 1-isoquinolinyl, 3-isoquinolinyl, etc.), tetrahydroquinolinyl (e.g., 1,2,3,4-tetrahydro-2-quinolyl, etc.), 1,2,3,4-tetrahydroisoquinolinyl (e.g., 1,2,3,4-tetrahydro-1-oxo-isoquinolinyl, etc.), quinoxalinyl, β-carbolinyl, 2-benzofurancarbonyl, 1-, 2-,4- or 5-benzimidazolyl, and the like. The term "cycloalkylalkoxycarbonyl" means an acyl group derived from a cycloalkylalkoxycarboxylic acid of the formula cycloalkylalkyl-O—COOH wherein cycloalkylalkyl has the meaning given above. The term "aryloxyalkanoyl" means an acyl radical of the formula aryl-O-alkanoyl wherein aryl and alkanoyl have the meaning given above. The term "heterocycloalkoxycarbonyl", means an acyl group derived from heterocyclyl-O—COOH wherein heterocyclyl is as defined above. The term "heterocycloalkylalkanoyl" is an acyl radical derived from a heterocycloalkyl-substituted alkylcarboxylic acid wherein heterocycloalkyl has the meaning given above. The term "heterocycloalkylalkoxycarbonyl" means an acyl radical derived from a heterocycloalkyl-substituted alkyl-O—COOH wherein heterocycloalkyl has the meaning given above. The term "heteroaryloxycarbonyl" means an acyl radical derived from a carboxylic acid represented by heteroaryl-O—COOH wherein heteroaryl has the meaning given above. The term "aminocarbonyl" alone or in combination, means an amino-substituted carbonyl (carbamoyl) group wherein the amino group can be a primary, secondary or tertiary amino group containing substituents selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl radicals and the like. The term "aminoalkanoyl" means an acyl group derived from an amino-substituted alkylcarboxylic acid wherein the amino group can be a primary, secondary or tertiary amino group containing substituents selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl radicals and the like. The term "halogen" means fluorine, chlorine, bromine or iodine. The term "haloalkyl" means an alkyl radical having the meaning as defined above wherein one or more hydrogens are replaced with a halogen. Examples of such haloalkyl radicals include chloromethyl, 1-bromoethyl, fluoromethyl, difluoromethyl, trifluoromethyl, 1,1,1-trifluoroethyl and the like. The term "leaving group" generally refers to groups readily displaceable by a nucleophile, such as an amine, a thiol or an alcohol nucleophile. Such leaving groups are well known in the art. Examples of such leaving groups include, but are not limited to, N-hydroxysuccinimide, N-hydroxybenzotriazole, halides, triflates, tosylates and the like. Preferred leaving groups are indicated herein where appropriate. The term "amino acid side chain" means the side chain group, including the stereochemistry of the carbon to which it is attached, attached to the naturally occurring amino acid which distinguishes the amino acid from glycine. For example, the amino acid side chain of alanine is methyl, of histidine is imidazolylmethyl and phenylalanine is benzyl, and the attachment of such side chains to the compound of this invention retain the naturally occurring stereochemistry of the carbon to which it is attached. The following example illustrates the definition:

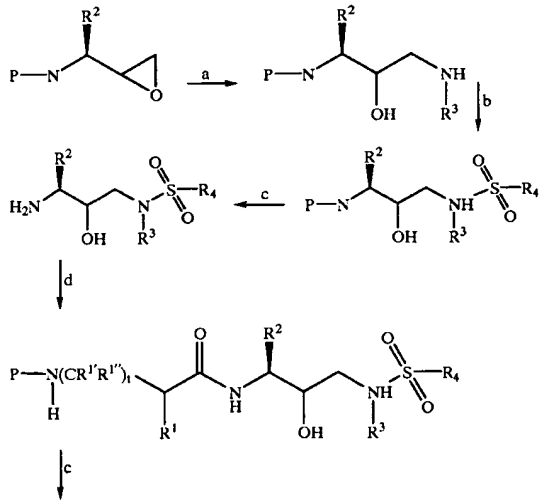


Procedures for preparing the compounds of Formula I are set forth below. It should be noted that the general procedure is shown as it relates to preparation of compounds having the specified stereochemistry, for example, wherein the absolute stereochemistry about the hydroxyl group is designated as (R). However, such procedures are generally applicable to those compounds of opposite configuration, e.g., where the stereochemistry about the hydroxyl group is (S). In addition, the compounds having the (R) stereochemistry can be utilized to produce those having the (S) stereochemistry. For example, a compound having the (R) stereochemistry can be inverted to the (S) stereochemistry using well-known methods.

Preparation of Compounds of Formula I

The compounds of the present invention represented by Formula I above can be prepared utilizing the following general procedure. This procedure is schematically shown in the following Schemes I and II:

SCHEME I



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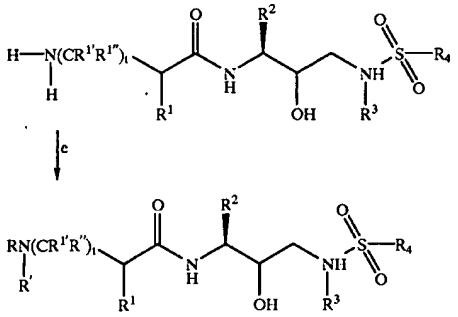
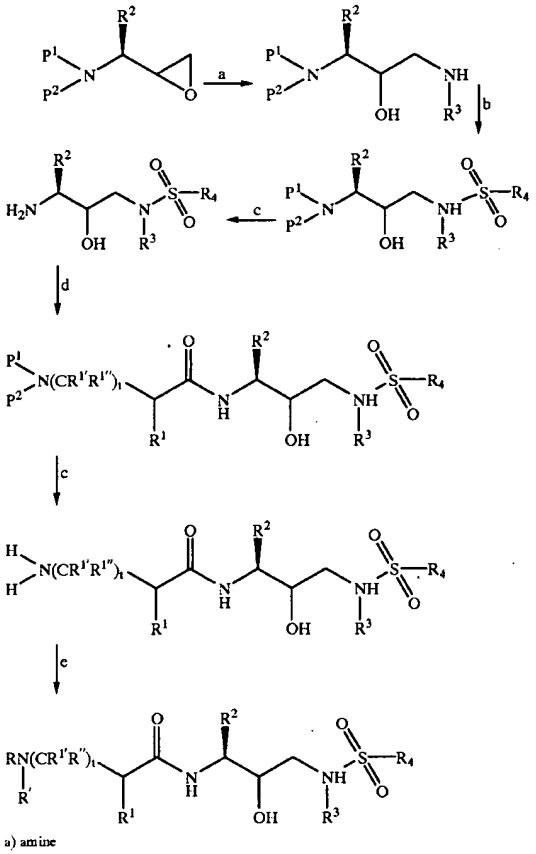


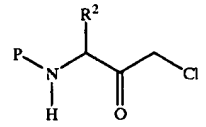
a) amine
b) sulfonyl chloride R^4SO_2Cl (or anhydride) + acid scavenger
c) deprotection
d) coupling
e) coupling.

SCHEME II



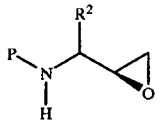
a) amine
b) sulfonyl chloride R^4SO_2Cl (or anhydride) + acid scavenger
c) deprotection
d) coupling
e) coupling.

An N-protected chloroketone derivative of an amino acid having the formula:



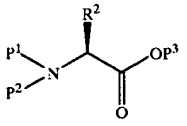
wherein P represents an amino protecting group, and R^2 is as defined above, is reduced to the corresponding alcohol utilizing an appropriate reducing agent. Suitable amino protecting groups are well known in the art and include carbobenzoxy, t-butoxycarbonyl, and the like. A preferred amino protecting group is carbobenzoxy. A preferred N-protected chloroketone is N-benzyloxycarbonyl-L-phenylalanine chloromethyl ketone. A preferred reducing agent is sodium borohydride. The reduction reaction is conducted at a temperature of from −10° C. to about 25° C., preferably at about 0° C., in a suitable solvent system such as, for example, tetrahydrofuran, and the like. The N-protected chloroketones are commercially available, e.g., such as from Bachem, Inc., Torrance, Calif. Alternatively, the chloroketones can be prepared by the procedure set forth in S. J. Fittkau, *J. Prakt. Chem.*, 315, 1037 (1973), and subsequently N-protected utilizing procedures which are well known in the art.

The halo alcohol can be utilized directly, as described below, or, preferably, is then reacted, preferably at room temperature, with a suitable base in a suitable solvent system to produce an N-protected amino epoxide of the formula:



wherein P and R^2 are as defined above. Suitable solvent systems for preparing the amino epoxide include ethanol, methanol, isopropanol, tetrahydrofuran, dioxane, and the like including mixtures thereof. Suitable bases for producing the epoxide from the reduced chloroketone include potassium hydroxide, sodium hydroxide, potassium t-butoxide, DBU and the like. A preferred base is potassium hydroxide.

Alternatively, a protected amino epoxide can be prepared, such as in co-owned and co-pending PCT Patent Application Ser. No. PCT/US93/04804 which is incorporated herein by reference, starting with an L-amino acid which is reacted with a suitable amino-protecting group in a suitable solvent to produce an amino-protected L-amino acid ester of the formula:



wherein P^3 represents carboxyl-protecting group, e.g., methyl, ethyl, benzyl, tertiary-butyl and the like; R^2 is as defined above; and P^1 and P^2 independently are selected from amine protecting groups, including but not limited to, arylalkyl, substituted arylalkyl, cycloalkenylalkyl and substituted cycloalkenylalkyl, allyl, substituted allyl, acyl, alkoxycarbonyl, aralkoxycarbonyl and silyl. Examples of arylalkyl include, but are not limited to benzyl,

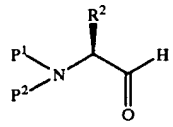
orthomethylbenzyl, trityl and benzhydryl, which can be optionally substituted with halogen, alkyl of C_1–C_8, alkoxy, hydroxy, nitro, alkylene, amino, alkylamino, acylamino and acyl, or their salts, such as phosphonium and ammonium salts. Examples of aryl groups include phenyl, naphthalenyl, indanyl, anthracenyl, durenyl, 9-(9-phenylfluorenyl) and phenanthrenyl, cycloalkenylalkyl or substituted cycloalkylenylalkyl radicals containing cycloalkyls of C_6–C_{10}. Suitable acyl groups include carbobenzoxy, t-butoxycarbonyl, iso-butoxycarbonyl, benzoyl, substituted benzoyl, butyryl, acetyl, tri-fluoroacetyl, tri-chloroacetyl, phthaloyl and the like.

Additionally, the P^1 and/or P^2 protecting groups can form a heterocyclic ring with the nitrogen to which they are attached, for example, 1,2-bis(methylene)benzene, phthalimidyl, succinimidyl, maleimidyl and the like and where these heterocyclic groups can further include adjoining aryl and cycloalkyl rings. In addition, the heterocyclic groups can be mono-, di- or tri-substituted, e.g., nitrophthalimidyl. The term silyl refers to a silicon atom optionally substituted by one or more alkyl, aryl and aralkyl groups.

Suitable silyl protecting groups include, but are not limited to, trimethylsilyl, triethylsilyl, tri-isopropylsilyl, tert-butyldimethylsilyl, dimethylphenylsilyl, 1,2-bis (dimethylsilyl)benzene, 1,2-bis(dimethylsilyl)ethane and diphenylmethylsilyl. Silylation of the amine functions to provide mono- or bis-disilylamine can provide derivatives of the aminoalcohol, amino acid, amino acid esters and amino acid amide. In the case of amino acids, amino acid esters and amino acid amides, reduction of the carbonyl function provides the required mono- or bis-silyl aminoalcohol. Silylation of the aminoalcohol can lead to the N,N,O-tri-silyl derivative. Removal of the silyl function from the silyl ether function is readily accomplished by treatment with, for example, a metal hydroxide or ammonium flouride reagent, either as a discrete reaction step or in situ during the preparation of the amino aldehyde reagent. Suitable silylating agents are, for example, trimethylsilyl chloride, tert-buty-dimethylsilyl chloride, phenyldimethylsilyl chlorie, diphenylmethylsilyl chloride or their combination products with imidazole or DMF. Methods for silylation of amines and removal of silyl protecting groups are well known to those skilled in the art. Methods of preparation of these amine derivatives from corresponding amino acids, amino acid amides or amino acid esters are also well known to those skilled in the art of organic chemistry including amino acid/amino acid ester or aminoalcohol chemistry.

Preferably P^1 and P^2 are independently selected from aralkyl and substituted aralkyl. More preferably, each of P^1 and P^2 is benzyl. As illustrated in the Examples below, P, P^1 and P^2 may serve as a nitrogen protecting group which is later removed in the preparation of compounds of this invention or may form a part of the final inhibitor structure. For example, benzoyl, benzyloxycarbonyl, t-butoxycarbonyl, pyridylmethoxycarbonyl, tetrahydrofuryloxycarbonyl, pyridylcarbonyl and the like can used to both protect a nitrogen from undergoing an undesired reaction and also be part of the structure of an active enzyme inhibitor.

The amino-protected L-amino acid ester is then reduced, to the corresponding alcohol. For example, the amino-protected L-amino acid ester can be reduced with diisobutylaluminum hydride at −78° C. in a suitable solvent such as toluene. Preferred reducing agents include lithium aluminium hydride, lithium borohydride, sodium borohydride, borane, lithium tri-ter-butoxyaluminum hydride, borane/THF complex. Most preferably, the reducing agent is diisobutylaluminum hydride (DiBAL-H) in toluene. The resulting alcohol is then converted, for example, by way of a Swern oxidation, to the corresponding aldehyde of the formula:



wherein P^1, P^2 and R^2 are as defined above. Thus, a dichloromethane solution of the alcohol is added to a cooled (−75 to −68° C.) solution of oxalyl chloride in dichloromethane and DMSO in dichloromethane and stirred for 35 minutes.

Acceptable oxidizing reagents include, for example, sulfur trioxide-pyridine complex and DMSO, oxalyl chloride and DMSO, acetyl chloride or anhydride and DMSO, trifluoroacetyl chloride or anhydride and DMSO, methanesulfonyl chloride and DMSO or tetrahydro thiaphene-S-oxide, toluenesulfonyl bromide and DMSO, trifluoromethanesulfonyl anhydride (triflic anhydride) and DMSO, phosphorus pentachloride and DMSO, dimethylphosphoryl chloride and DMSO and isobutyl chloroformate and DMSO. The oxidation conditions reported by Reetz et al [*Angew Chem.*, 99, p. 1186, (1987)], *Angew Chem. Int. Ed. Engl.*, 26, p. 1141, 1987) employed oxalyl chloride and DMSO at −78° C.

The preferred oxidation method described in this invention is sulfur trioxide pyridine complex, triethylamine and DMSO at room temperature. This system provides excellent yields of the desired chiral protected amino aldehyde usable without the need for purification i.e., the need to purify kilograms of intermediates by chromatography is eliminated and large scale operations are made less hazardous. Reaction at room temperature also eliminated the need for the use of low temperature reactor which makes the process more suitable for commercial production.

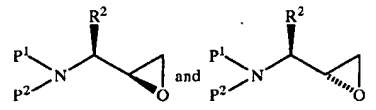
The reaction may be carried out under and inert atmosphere such as nitrogen or argon, or normal or dry air, under atmospheric pressure or in a sealed reaction vessel under positive pressure. Preferred is a nitrogen atmosphere. Alternative amine bases include, for example, tri-butyl amine, tri-isopropyl amine, N-methylpiperidine, N-methyl morpholine, azabicyclononane, diisopropylethylamine, 2,2,6,6-tetramethylpiperidine, N,N-dimethylaminopyridine, or mixtures of these bases. Triethylamine is a preferred base. Alternatives to pure DMSO as solvent include mixtures of DMSO with non-protic or halogenated solvents such as tetrahydrofuran, ethyl acetate, toluene, xylene, dichloromethane, ethylene dichloride and the like. Dipolar aprotic co-solvents include acetonitrile, dimethylformamide, dimethylacetamide, acetamide, tetramethyl urea and its cyclic analog, N-methylpyrrolidone, sulfolane and the like. Rather than N,N-dibenzylphenylalaninol as the aldehyde precursor, the phenylalaninol derivatives discussed above can be used to provide the corresponding N-monosubstituted [either P^1 or P^2=H] or N,N-disubstituted aldehyde.

In addition, hydride reduction of an amide or ester derivative of the corresponding alkyl, benzyl or cycloalkenyl nitrogen protected phenylalanine, substituted phenylalanine or cycloalkyl analog of phenyalanine derivative can be carried out to provide the aldehydes. Hydride transfer is an additional method of aldehyde synthesis under conditions where aldehyde condensations are avoided, cf, Oppenauer Oxidation.

The aldehydes of this process can also be prepared by methods of reducing protected phenylalanine and phenylalanine analogs or their amide or ester derivatives by, e.g., sodium amalgam with HCl in ethanol or lithium or sodium or potassium or calcium in ammonia. The reaction temperature may be from about −20° C. to about 45° C., and preferably from abut 5° C. to about 25° C. Two additional methods of obtaining the nitrogen protected aldehyde include oxidation of the corresponding alcohol with bleach in the presence of a catalytic amount of 2,2,6,6-tetramethyl-1-pyridyloxy free radical. In a second method, oxidation of the alcohol to the aldehyde is accomplished by a catalytic amount of tetrapropylammonium perruthenate in the presence of N-methylmorpholine-N-oxide.

Alternatively, an acid chloride derivative of a protected phenylalanine or phenylalanine derivative as disclosed above can be reduced with hydrogen and a catalyst such as Pd on barium carbonate or barium sulphate, with or without an additional catalyst moderating agent such as sulfur or a thiol (Rosenmund Reduction).

The aldehyde resulting from the Swern oxidation is then reacted with a halomethyllithium reagent, which reagent is generated in situ by reacting an alkyllithium or arylithium compound with a dihalomethane represented by the formula $X^1CH_2X^2$ wherein X^1 and X^2 independently represent I, Br or Cl. For example, a solution of the aldehyde and chloroiodomethane in THF is cooled to −78° C. and a solution of n-butyllithium in hexane is added. The resulting product is a mixture of diastereomers of the corresponding amino-protected epoxides of the formulas:



The diastereomers can be separated e.g., by chromatography, or, alternatively, once reacted in subsequent steps the diastereomeric products can be separated. For compounds having the (S) stereochemistry, a D-amino acid can be utilized in place of the L-amino acid.

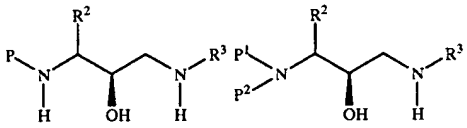
The addition of chloromethylithium or bromomethylithium to a chiral amino aldehyde is highly diastereoselective. Preferably, the chloromethyllithium or bromomethylithium is generated in-situ from the reaction of the dihalomethane and n-butyllithium. Acceptable methyleneating halomethanes include chloroiodomethane, bromochloromethane, dibromomethane, diiodomethane, bromofluoromethane and the like. The sulfonate ester of the addition product of, for example, hydrogen bromide to formaldehyde is also a methyleneating agent. Tetrahydrofuran is the preferred solvent, however alternative solvents such as toluene, dimethoxyethane, ethylene dichloride, methylene chloride can be used as pure solvents or as a mixture. Dipolar aprotic solvents such as acetonitrile, DMF, N-methylpyrrolidone are useful as solvents or as part of a solvent mixture. The reaction can be carried out under an inert atmosphere such as nitrogen or argon. For n-butyl lithium can be substituted other organometalic reagents reagents such as methyllithium, tert-butyl lithium, sec-butyl lithium, phenyllithium, phenyl sodium and the like. The reaction can be carried out at temperatures of between about −80° C. to 0° C. but preferably between about −80° C. to −20° C. The most preferred reaction temperatures are between −40° C. to −15° C. Reagents can be added singly but multiple additions are preferred in certain conditions. The preferred pressure of the reaction is atmospheric however a positive pressure is valuable under certain conditions such as a high humidity environment.

Alternative methods of conversion to the epoxides of this invention include substitution of other charged methylenation precurser species followed by their treatment with base to form the analogous anion. Examples of these species include trimethylsulfoxonium tosylate or triflate, tetramethylammonium halide, methyldiphenylsulfoxonium halide wherein halide is chloride, bromide or iodide.

The conversion of the aldehydes of this invention into their epoxide derivative can also be carried out in multiple steps. For example, the addition of the anion of thioanisole prepared from, for example, a butyl or aryl lithium reagent, to the protected aminoaldehyde, oxidation of the resulting protected aminosulfide alcohol with well known oxidizing agents such as hydrogen peroxide, tert-butyl hypochlorite, bleach or sodium periodate to give a sulfoxide. Alkylation of the sulfoxide with, for example, methyl iodide or bromide, methyl tosylate, methyl mesylate, methyl triflate, ethyl bromide, isopropyl bromide, benzyl chloride or the like, in the presence of an organic or inorganic base. Alternatively, the protected aminosulfide alcohol can be alkylated with, for example, the alkylating agents above, to provide a sulfonium salts that are subsequently converted into the subject epoxides with tert-amine or mineral bases.

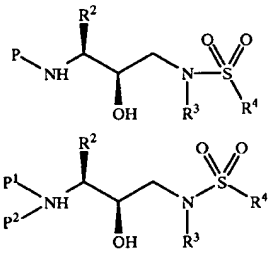
The desired epoxides formed, using most preferred conditions, diastereoselectively in ratio amounts of at least about an 85:15 ratio (S:R). The product can be purified by chromatography to give the diastereomerically and enantiomerically pure product but it is more conveniently used directly without purification to prepare retroviral protease inhibitors. The foregoing process is applicable to mixtures of optical isomers as well as resolved compounds. If a particular optical isomer is desired, it can be selected by the choice of starting material, e.g., L-phenylalanine, D-phenylalanine, L-phenylalaninol, D-phenylalaninol, D-hexahydrophenylalaninol and the like, or resolution can occur at intermediate or final steps. Chiral auxiliaries such as one or two equivilants of camphor sulfonic acid, citric acid, camphoric acid, 2-methoxyphenylacetic acid and the like can be used to form salts, esters or amides of the compounds of this invention. These compounds or derivatives can be crystallized or separated chromatographically using either a chiral or achiral column as is well known to those skilled in the art.

The amino epoxide is then reacted, in a suitable solvent system, with an equal amount, or preferably an excess of, a desired amine of the formula R^3NH_2, wherein R^3 is hydrogen or is as defined above. The reaction can be conducted over a wide range of temperatures, e.g., from about 10° C. to about 100° C., but is preferably, but not necessarily, conducted at a temperature at which the solvent begins to reflux. Suitable solvent systems include protic, non-protic and dipolar aprotic organic solvents such as, for example, those wherein the solvent is an alcohol, such as methanol, ethanol, isopropanol, and the like, ethers such as tetrahydrofuran, dioxane and the like, and toluene, N,N-dimethylformamide, dimethyl sulfoxide, and mixtures thereof. A preferred solvent is isopropanol. Exemplary amines corresponding to the formula R^3NH_2 include benzyl amine, isobutylamine, n-butyl amine, isopentyl amine, isoamylamine, cyclohexanemethyl amine, naphthylene methyl amine and the like. The resulting product is a 3-(N-protected amino)-3-(R^2)-1-(NHR^3)-propan-2-ol derivative (hereinafter referred to as an amino alcohol) can be represented by the formulas:



wherein P, P^1, P^2, R^2 and R^3 are as described above. Alternatively, a haloalcohol can be utilized in place of the amino epoxide.

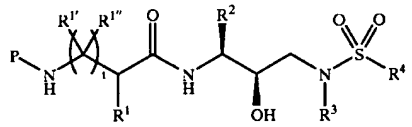
The amino alcohol defined above is then reacted in a suitable solvent with a sulfonyl chloride (R^4SO_2Cl) or sulfonyl anhydride in the presence of an acid scavenger. Suitable solvents in which the reaction can be conducted include methylene chloride, tetrahydrofuran. Suitable acid scavengers include triethylamine, pyridine. Preferred sulfonyl chlorides are methanesulfonyl chloride and benzenesulfonyl chloride. The resulting sulfonamide derivative can be represented, depending on the epoxide utilized by the formulas



wherein P, P^1, P^2, R^2, R^3 and R^4 are as defined above. These intermediates are useful for preparing inhibitor compounds of the present invention and are also active inhibitors of retroviral proteases.

The sulfonyl halides of the formula R^4SO_2X can be prepared by the reaction of a suitable Grignard or alkyl lithium reagent with sulfuryl chloride, or sulfur dioxide followed by oxidation with a halogen, preferably chlorine. Also, thiols may be oxidized to sulfonyl chlorides using chlorine in the presence of water under carefully controlled conditions. Additionally, sulfonic acids may be converted to sulfonyl halides using reagents such as PCl_5, and also to anhydrides using suitable dehydrating reagents. The sulfonic acids may in turn be prepared using procedures well known in the art. Such sulfonic acids are also commercially available. In place of the sulfonyl halides, sulfinyl halides (R^4SOX) or sulfenyl halides (R^4SX) can be utilized to prepare compounds wherein the —SO_2— moiety is replaced by an —SO— or —S— moiety, respectively.

Following preparation of the sulfonamide derivative, the amino protecting group P or P^1 and P^2 amino protecting groups are removed under conditions which will not affect the remaining portion of the molecule. These methods are well known in the art and include acid hydrolysis, hydrogenolysis and the like. A preferred method involves removal of the protecting group, e.g., removal of a carbobenzoxy group, by hydrogenolysis utilizing palladium on carbon in a suitable solvent system such as an alcohol, acetic acid, and the like or mixtures thereof. Where the protecting group is a t-butoxycarbonyl group, it can be removed utilizing an inorganic or organic acid, e.g., HCl or trifluoroacetic acid, in a suitable solvent system, e.g., dioxane or methylene chloride. The resulting product is the amine salt derivative. Following neutralization of the salt, the amine is then reacted with an amino acid or corresponding derivative thereof represented by the formula (PN[$CR^{1'}R^{1''}$], $CH(R^1)$ COOH) wherein t, R^1, $R^{1'}$ and $R^{1''}$ are as defined above, to produce the antiviral compounds of the present invention having the formula:



wherein t, P, R^1, $R^{1'}$, $R^{1''}$, R^2, R^3 and R^4 are as defined above. Preferred protecting groups in this instance are a benzyloxycarbonyl group or a t-butoxycarbonyl group. Where t is O and R^1 is alkyl, alkenyl, alkynyl, cycloalkyl, —$CH_2SO_2NH_2$, —$CH_2CO_2CH_3$, —CO_2CH_3, —$CONH_2$, —$CH_2C(O)NHCH_3$, —$C(CH_3)_2(SH)$, —$C(CH_3)_2(SCH_3)$, —$C(CH_3)_2[S(O)CH_3]$, —$C(CH_3)_2[S(O_2)CH_3]$, or an amino acid side chain, such materials are well known and many are commercially available from Sigma-Aldrich.

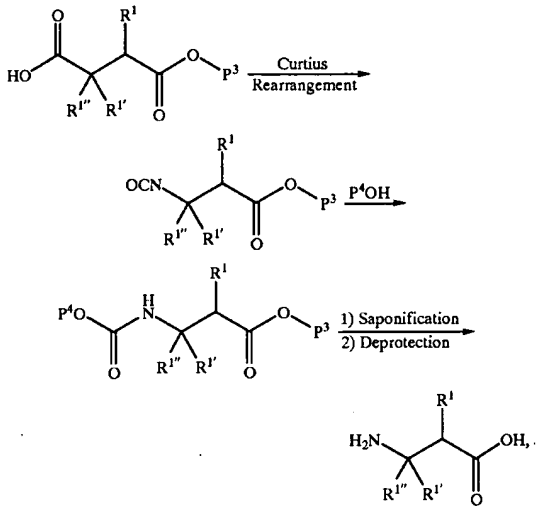
Where the amine is reacted with a derivative of an amino acid, e.g., when t=1, so that the amino acid is a β-amino acid, such β-amino acids can be prepared according to the procedure set forth in a co-owned, copending patent application, U.S. Ser. No. 07/853,561 or the following procedures.

Various methods have been proposed for the preparation of chiral β-amino acids. See, for example, *Chemistry and Biochemistry of Amino Acids,* Vol. 4, Chapter 5, pp. 250–57, B. Weinstein, Ed., Dekker, N.Y. (1975). Furukawa et al, *Chem. Pharm. Bull.,* 25, 1319 (1977), disclose asymmetric synthesis of β-amino acids by addition of chiral amines to carbon-carbon double bonds having nitrile or ester groups in the α-position. However, optical purities of the β-amino acids thus produced range from 2 to 19%. Furukawa et al also report that optically active β-amino acids have been produced with optical purities ranging from 2 to 28% by reacting chiral Schiff bases with Reformsky reagent. Terentev et al, Dohl. Ahad. Nauh SSR, 163,674 (1965) disclose synthesis of β-aminobutyric acids involving addition of chiral amines to crotonic acid with optical purities ranging from 7–9%.

Brown et al, *Tetrahedron Lett.,* Vol. 28, No. 19, pp 2179–2182 (1987), disclose a method of preparing optically active disubstituted β-amino acids which involves asymmetric catalytic hydrogenation of N-substituted α-(aminoalkyl) acrylates. In order to verify the stereochemistry of the product, Curtius rearrangement was effected on the monomethyl ester of optically enriched RR-anti-2,3-dimethylsuccinic acid and trapping of the incipient isocyanate derivative with tertiary alcohol, namely, t-butyl alcohol, to give the corresponding R-enriched β-amino acid. Ninomita et al, *Tetrahedron Lett.,* Vol. 30, 2152–2157 (1975) studied the Curtius rearrangement utilizing benzoic acid, diphenylphosphoryl azide and triethylamine followed by treatment with various alcohols and found that t-butyl alcohol gives yields superior to benzyl alcohol, ethanol and phenol.

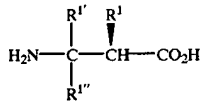
Utilization of a primary or secondary alcohol to trap an isocyanate derivative of a chiral mono-substituted succinate, and, in particular, in a Curtius rearrangement of a chiral mono-substituted succinate, to produce chiral β-amino acids significantly increases the overall yield. The resulting carbamate-protected β-amino esters are then saponified to produce the corresponding carbamate-protected β-amino acids which are then deprotected to produce β-amino acids possessing the same absolute configuration as naturally-

occurring (L)-amino acids. The overall reaction sequence can be shown as follow:

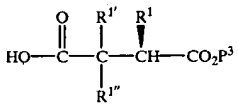


wherein R^1, $R^{1'}$, $R^{1''}$, and P^3 are as defined above and P^4OH are preferably represents radicals derived from primary and secondary alcohols.

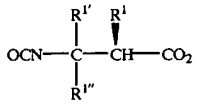
This process can also be used in the asymetric synthesis of β-amino acids represented by the formula:



wherein R^1, $R^{1'}$ and $R^{1''}$ are as defined above. Such compounds are formed by Curtius rearrangement of 2(R)-substituted succinates represented by the formula

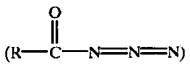


wherein R^1, $R^{1'}$, $R^{1''}$ and P^3 are as defined above, to afford the isocyanate derivative:



Using 2(S)-substituted succinates, 2(S)-substituted β-amino acids can also be prepared stereospecifically.

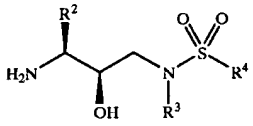
Curtius rearrangement involves pyrolysis of acyol azides



to yield isocyanates (R—N=C=O) which can be subsequently hydrolyzed to give amines. See March, Advanced Organic Chemistry, p. 1005, 2nd ed (1977). As a general rule, Curtius rearrangement is a concerted reaction and therefore proceeds with retention of configuration of the starting materials. Determination of specific reaction conditions for effecting Curtius rearrangements of various succinates is within the skill of one in the art familiar with such reactions. In the method of the present invention, Curtius rearrangement to afford the desired isocyante is preferably effected by treating a 2-substituted succinate with one equivalent of diphenoxyphosphoryl azide $(PhO)_2PON_3$ and triethylamine to form the acyl azide followed by heating in an inert solvent, such as in warm toluene, preferably at about 80° C. for about three hours, to afford the isocyante derivative.

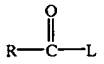
Suitable primary and secondary alcohols include those represented by the formula P^4OH where P^4 represents substituted and unsubstituted alkyl, cycloalkyl, aralkyl and aryl radicals, as well as suitable equivalents such as, for example, silyl radicals. Preferably, the primary and secondary alcohols are those wherein P^4 represents substituted and unsubstituted, straight chain as well as branched chain, alkyl radicals having from 1 to about 12 carbon atoms, substituted and unsubstituted cycloalkyl radicals having from 4 to about 7 carbon atoms, and substituted and unsubstituted aryl, alkaryl and aralkyl radicals. Examples of such suitable alcohols include benzyl alcohol, isopropyl alcohol, 4-methoxybenzyl alcohol, 2-trimethylsilylethanol, fluorenyl methanol and benzhydrol. Preferred alcohols are benzyl alcohol and 4-methoxybenzyl alcohol. Other primary and secondary alcohols suitable for use in the practice of the present invention will be readily apparent to those skilled in the art.

The ester derivative is then saponified by any one of numerous well-known procedures, such as by treatment with aqueous lithium hydroxide/THF (tetrahydrofuran), preferably for three hours at 0° C. The resultant product is the corresponding carbamate-protected β-amino acids. These are subsequently deprotected by any one of several well-known procedures, such as by acid catalyzed hydrolysis or by hydrogenolysis, to produce the corresponding deprotected β-amino acids. Alternatively, the carbamate-protected β-amino acid can be coupled to the amine



followed by deprotection and incorporation of R and R'.

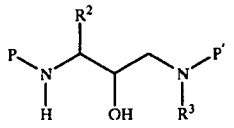
The N-protecting group can be subsequently removed, if desired, utilizing the procedures described above, and then reacted with a carboxylate represented by the formula



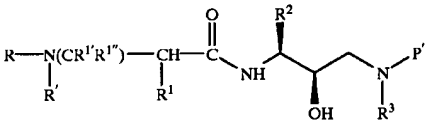
wherein R is as defined above and L is an appropriate leaving group such as a halide. Preferably, where R^1 is a side chain of a naturally occurring α-amino acid, R is a 2-quinoline carbonyl group derived from N-hydroxysuccinimide-2-quinoline carboxylate, i.e., L is hydroxy succinimide. A solution of the free amine (or amine acetate salt) and about 1.0 equivalent of the carboxylate are mixed in an appropriate solvent system and optionally treated with up to five equivalents of a base such as, for example, N-methylmorpholine, at about room temperature.

Appropriate solvent systems include tetrahydrofuran, methylene chloride or N,N-dimethyl formamide, and the like, including mixtures thereof.

Alternatively, the protected amino alcohol from the epoxide opening can be further protected at the newly introduced amino group with a protecting group P' which is not removed when the first protecting P is removed. One skilled in the art can choose appropriate combinations of P and P'. One suitable choice is when P is Cbz and P' is Boc. The resulting compound represented by the formula:



can be carried through the remainder of the synthesis to provide a compound of the formula:



and the new protecting group P' is selectively removed, and following deprotection, the resulting amine reacted to form the sulfonamide derivative as described above. This selective deprotection and conversion to the sulfonamide can be accomplished at either the end of the synthesis or at any appropriate intermediate step if desired.

The thiocarbonyl compounds of this invention are really prepared by methods well known to those skilled in the art, for example, by treatment of a carbonyl compound with Lawesson's reagent (2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide) which is an article of commerce. Phosphorus pentasulfide may also be used or one can treat an amine of this invention with a pre-formed thiocarbonyl reagent such as thiocarbonylchlorid in the presence of base.

In place of the sulfonyl halides, sulfinyl halides (RSOCl) and sulfenyl halides (RSCl) can be utilized to prepare compounds wherein the —SO_2— moiey is replaced by —SO— or —S—, respectively.

It is contemplated that for preparing compounds of the Formulas having R^6, the compounds can be prepared following the procedure set forth above and, prior to coupling the sulfonamide derivative or analog thereof, e.g. coupling to the amino acid $PNH(CH_2)_tCH(R^1)COOH$, carried through a procedure referred to in the art as reductive amination. Thus, a sodium cyanoborohydride and an appropriate aldehyde or ketone can be reacted with the sulfonamide derivative compound or appropriate analog at room temperature in order to reductively aminate any of the compounds of Formulas I–IV. It is also contemplated that where R^3 of the amino alcohol intermediate is hydrogen, the inhibitor compounds of the present invention wherein R^3 is alkyl, or other substituents wherein the α-C contains at least one hydrogen, can be prepared through reductive amination of the final product of the reaction between the amino alcohol and the amine or at any other stage of the synthesis for preparing the inhibitor compounds.

Contemplated equivalents of the general formulas set forth above for the antiviral compounds and derivatives as well as the intermediates are compounds otherwise corresponding thereto and having the same general properties, such as tautomers thereof as well as compounds, wherein one or more of the various R groups are simple variations of the substituents as defined therein, e.g., wherein R is a higher alkyl group than that indicated. In addition, where a substituent is designated as, or can be, a hydrogen, the exact chemical nature of a substituent which is other than hydrogen at that position, e.g., a hydrocarbyl radical or a halogen, hydroxy, amino and the like functional group, is not critical so long as it does not adversely affect the overall activity and/or synthesis procedure.

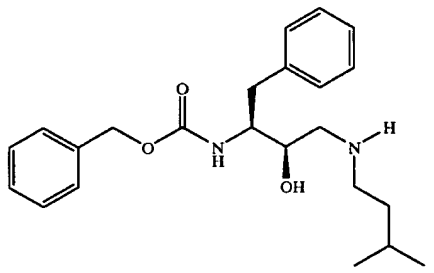
The chemical reactions described above are generally disclosed in terms of their broadest application to the preparation of the compounds of this invention. Occasionally, the reactions may not be applicable as described to each compound included within the disclosed scope. The compounds for which this occurs will be readily recognized by those skilled in the art. In all such cases, either the reactions can be successfully performed by conventional modifications known to those skilled in the art, e.g., by appropriate protection of interfering groups, by changing to alternative conventional reagents, by routine modification of reaction conditions, and the like, or other reactions disclosed herein or otherwise conventional, will be applicable to the preparation of the corresponding compounds of this invention. In all preparative methods, all starting materials are known or readily preparable from known starting materials.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

All reagents were used as received without purification. All proton and carbon NMR spectra were obtained on either a Varian VXR-300 or VXR-400 nuclear magnetic resonance spectrometer.

The following Examples 1 through 9 illustrate preparation of intermediates. These intermediates are useful in preparing the inhibitor compounds of the present invention as illustrated in Examples 10–16. In addition, the intermediates of Examples 2–6 are also retroviral protease inhibitors and inhibit, in particular, HIV protease.

EXAMPLE 1A



Preparation of N[3(S)-benzyloxycarbonylamino-2 (R)-hydroxy-4-phenylbutyl]-N-isoamylamine

Part A

To a solution of 75.0 g (0.226 mol) of N-benzyloxycarbonyl-L-phenylalanine chloromethyl ketone in a mixture of 807 mL of methanol and 807 mL of tetrahydrofuran at −2° C., was added 13.17 g (0.348 mol, 1.54 equiv.) of solid sodium borohydride over one hundred

minutes. The solvents were removed under reduced pressure at 40° C. and the residue dissolved in ethyl acetate (approx. 1 L). The solution was washed sequentially with 1M potassium hydrogen sulfate, saturated sodium bicarbonate and then saturated sodium chloride solutions. After drying over anhydrous magnesium sulfate and filtering, the solution was removed under reduced pressure. To the resulting oil was added hexane (approx. 1 L) and the mixture warmed to 60° C. with swirling. After cooling to room temperature, the solids were collected and washed with 2 L of hexane. The resulting solid was recrystallized from hot ethyl acetate and hexane to afford 32.3 g (43% yield) of N-benzyloxycarbonyl-3(S)-amino-1-chloro-4-phenyl-2(S)-butanol, mp 150–151° C. and M+Li⁺=340.

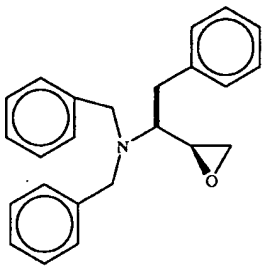
Part B

To a solution of 6.52 g (0.116 mol, 1.2 equiv.) of potassium hydroxide in 968 mL of absolute ethanol at room temperature, was added 32.3 g (0.097 mol) of N-CBZ-3(S)-amino-1-chloro-4-phenyl-2(S)-butanol. After stirring for fifteen minutes, the solvent was removed under reduced pressure and the solids dissolved in methylene chloride. After washing with water, drying over magnesium sulfate, filtering and stripping, one obtains 27.9 g of a white solid. Recrystallization from hot ethyl acetate and hexane afforded 22.3 g (77% yield) of N-benzyloxycarbonyl-3(S)-amino-1,2(S)-epoxy-4phenylbutane, mp 102–103° C. and MH⁺ 298.

Part C

A solution of N-benzyloxycarbonyl 3(S)-amino-1,2-(S)-epoxy-4-phenylbutane (1.00 g, 3.36 mmol) and isoamylamine (4.90 g, 67.2 mmol, 20 equiv.) in 10 mL of isopropyl alcohol was heated to reflux for 1.5 hours. The solution was cooled to room temperature, concentrated in vacuo and then poured into 100 mL of stirring hexane whereupon the product crystallized from solution. The product was isolated by filtration and air dried to give 1.18 g, 95% of N=[[3(S)-phenylmethylcarbamoyl)amino-2(R)-hydroxy-4-phenylbutyl]N-[(3-methylbutyl)]amine mp 108.0–109.5° C., MH⁺ m/z=371.

EXAMPLE 1B



Preparation of N,N-dibenzyl-3(S)-amino-1,2-(S)-epoxy-4-phenylbutane

Step A

A solution of L-phenylalanine (50.0 g, 0.302 mol), sodium hydroxide (24.2 g, 0.605 mol) and potassium carbonate (83.6 g, 0.605 mol) in water (500 ml) was heated to 97° C. Benzyl bromide (108.5 ml, 0.912 mol) was then slowly added (addition time ~25 min). The mixture was then stirred at 97° C. for 30 minutes. The solution was cooled to room temperature and extracted with toluene (2x250 ml). The combined organic layers were then washed with water, brine, dried over magnesium sulfate, filtered and concentrated to give an oil product. The crude product was then used in the next step without purification.

Step B

The crude benzylated product of the above step was dissolved in toluene (750 ml) and cooled to −55° C. A 1.5 M solution of DIBAL-H in toluene (443.9 ml, 0.666 mol) was then added at a rate to maintain the temperature between −55° to −50° C. (addition time ~1 hour). The mixture was stirred for 20 minutes at −55° C. The reaction was quenched at −55° C. by the slow addition of methanol (37 ml). The cold solution was then poured into cold (5° C.) 1.5 N HCl solution (1.8 L). The precipitated solid (approx. 138 g) was filtered off and washed with toluene. The solid material was suspended in a mixture of toluene (400 ml) and water (100 ml). The mixture was cooled to 5° C., treated with 2.5 N NaOH (186 ml) and then stirred at room temperature until the solid was dissolved. The toluene layer was separated from the aqueous phase and washed with water and brine, dried over magnesium sulfate, filtered and concentrated to a volume of 75 ml (89 g). Ethyl acetate (25 ml) and hexane (25 ml) were then added to the residue upon which the alcohol product began to crystallize. After 30 min., an additional 50 ml hexane was added to promote further crystallization. The solid was filtered off and washed with 50 ml hexane to give approximately 35 g of material. A second crop of material could be isolated by refiltering the mother liquor. The solids were combined and recrystallized from ethyl acetate (20 ml) and hexane (30 ml) to give, in 2 crops, approximately 40 g (40% from L-phenylalanine) of analytically pure alcohol product. The mother liquors were combined and concentrated (34 g). The residue was treated with ethyl acetate and hexane which provided an additional 17 g (~7% yield) of slightly impure solid product. Further optimization in the recovery from the mother liquor is probable.

Alternatively, the alcohol was prepared from L-phenylalaninol. L-phenylalaninol (176.6 g, 1.168 mol) was added to a stirred solution of potassium carbonate (484.6 g, 3.506 mol) in 710 mL of water. The mixture was heated to 65° C. under a nitrogen atmosphere. A solution of benzyl bromide (400 g, 2.339 mol) in 3 A ethanol (305 mL) was added at a rate that maintained the temperature between 60–68° C. The biphasic solution was stirred at 65° C. for 55 min and then allowed to cool to 10° C. with vigorous stirring. The oily product solidified into small granules. The product was diluted with 2.0 L of tap water and stirred for 5 minutes to dissolve the inorganic by products. The product was isolated by filtration under reduced pressure and washed with water until the pH is 7. The crude product obtained was air dried overnite to give a semi-dry solid (407 g) which was recrystallized from 1.1 L of ethyl acetate/heptane (1:10 by volume). The product was isolated by filtration (at −8° C.), washed with 1.6 L of cold (−10° C.) ethyl acetate/heptane (1:10 by volume) and air-dried to give 339 g (88% yield) of βS-2-[Bis(phenylmethyl)amino]benzene-propanol, mp 71.5–73.0° C. More product can be obtained from the mother liquor if necessary. The other analytical characterization was identical to compound prepared as described above.

Step C

A solution of oxalyl chloride (8.4 ml, 0.096 mol) in dichloromethane (240 ml) was cooled to −74° C. A solution of DMSO (12.0 ml, 0.155 mol) in dichloromethane (50 ml) was then slowly added at a rate to maintain the temperature at −74° C. (addition time ~1.25 hr). The mixture was stirred for 5 min. followed by addition of a solution of the alcohol (0.074 mol) in 100 ml of dichloromethane (addition time ~20 min., temp. −75° C. to −68° C.). The solution was stirred at −78° C. for 35 minutes. Triethylamine (41.2 ml, 0.295 mol) was then added over 10 min. (temp. −78° to −68°

C.) upon which the ammonium salt precipitated. The cold mixture was stirred for 30 min. and then water (225 ml) was added. The dichloromethane layer was separated from the aqueous phase and washed with water, brine, dried over magnesium sulfate, filtered and concentrated. The residue was diluted with ethyl acetate and hexane and then filtered to further remove the ammonium salt. The filtrate was concentrated to give the desired aldehyde product. The aldehyde was carried on to the next step without purification.

Temperatures higher than −70° C. have been reported in the literature for the Swern oxidation. Other Swern modifications and alternatives to the Swern oxidations are also possible.

Alternatively, the aldehyde was prepared as follows. (200 g, 0.604 ml) was dissolved in triethylamine (300 mL, 2.15 mol). The mixture was cooled to 12° C. and a solution of sulfur trioxide/pyridine complex (380 g, 2.39 mol) in DMSO (1.6 L) was added at a rate to maintain the temperature between 8–17° C. (addition time−1.0 h). The solution was stirred at ambient temperature under a nitrogen atmosphere for 1.5 hour at which time the reaction was complete by TTC analysis (33% ethyl acetate/hexane, silica gel). The reaction mixture was cooled with ice water and quenced with 1.6 L of cold water (10–15° C.) over 45 minutes. The resultant solution was extracted with ethyl acetate (2.0 L), washed with 5% citric acid (2.0 L), and brine (2.2 L), dried over $MgSO_4$ (280 g) and filtered. The solvent was removed on a rotary evaporator at 35–40° C. and then dried under vaccuum to give 198.8 g of αS-[Bis-(phenylmethyl)amino] benzenepropanaldehyde as a pale yellow oil (99.9%). The crude product obtained was pure enough to be used directly in the next step without purification. The analytical data of the compound were consistent with the published literature. $[\alpha]_D25$=−92.9° (c 1.87, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) ∂, 2.94 and 3.15 (ABX-System, 2H, J_{AB}=13.9 Hz, J_{AX}=7.3 Hz and J_{BX}=6.2 Hz), 3.56 (t, 1H, 7.1 Hz), 3.69 and 3.82 (AB-System, 4H, J_{AB}=13.7 Hz), 7.25 (m, 15 H) and 9.72 (s, 1H); HRMS calcd for (M+1) $C_{23}H_{24}NO$ 330.450, found: 330.1836. Anal. Calcd. for $C_{23}H_{23}ON$: C, 83.86; H, 7.04; N, 4.25. Found: C, 83.64; H, 7.42; N, 4.19. HPLC on chiral stationary phase: (S,S) Pirkle-Whelk-O 1 column (250×4.6 mm I.D.), mobile phase: hexane/isopropanol (99.5:0.5, v/v), flow-rate: 1.5 ml/min, detection with UV detector at 210 nm. Retention time of the desired S-isomer: 8.75 min., retention time of the R-enanatiomer 10.62 min.

Step D

A solution of αS-[Bis(phenylmethyl)amino]benzenepropanaldehyde (191.7 g, 0.58 mol) and chloroiodomethane (56.4 mL, 0.77 mol) in tetrahydrofuran (1.8 L) was cooled to −30 to −35° C. (colder temperature such as −70° C. also worked well but warmer temperatures are more readily achieved in large scale operations) in a stainless steel reactor under a nitrogen atmosphere. A solution of n-butyllithium in hexane (1.6 M, 365 mL, 0.58 mol) was then added at a rate that maintained the temperature below −25° C. After addition the mixture was stirred at −30 to −35° C. for 10 minutes. More additions of reagents were carried out in the following manner: (1) additional chloroiodomethane (17 mL) was added, followed by n-butyllithium (110 mL) at <−25° C. After addition the mixture was stirred at −30 to −35° C. for 10 minutes. This was repeated once. (2) Additional chloroiodomethane (8.5 mL, 0.11 mol) was added, followed by n-butyllithium (55 mL, 0.088 mol) at <−25° C. After addition, the mixture was stirred at −30 to −35° C. for 10 minutes. This was repeated 5 times. (3) Additional chloroiodomethane (8.5 mL, 0.11 mol) was added, followed by n-butyllithium (37 mL, 0.059 mol) at <−25° C. After addition, the mixture was stirred at −30 to −35° C. for 10 minutes. This was repeated once. The external cooling was stopped and the mixture warmed to ambient temp. over 4 to 16 hours when TLC (silica gel, 20% ethyl acetate/hexane) indicated that the reaction was completed. The reaction mixture was cooled to 10° C. and quenched with 1452 g of 16% ammonium chloride solution (prepared by dissolving 232 g of ammonium chloride in 1220 mL of water), keeping the temperature below 23° C. The mixture was stirred for 10 minutes and the organic and aqueous layers were separated. The aqueous phase was extracted with ethyl acetate (2×500 mL). The ethyl acetate layer was combined with the tetrahydrofuran layer. The combined solution was dried over magnesium sulfate (220 g), filtered and concentrated on a rotary evaporator at 65° C. The brown oil residue was dried at 70° C. in vacuo (0.8 bar) for 1 h to give 222.8 g of crude material. (The crude product weight was >100%. Due to the relative instability of the product on silica gel, the crude product is usually used directly in the next step without purification). The diastereomeric ratio of the crude mixture was determined by proton NMR: (2S)/(2R): 86:14. The minor and major epoxide diastereomers were characterized in this mixture by tlc analysis (silica gel, 10% ethyl acetate/hexane), Rf=0.29 & 0.32, respectively. An analytical sample of each of the diastereomers was obtained by purification on silica-gel chromatography (3% ethyl acetate/hexane) and characterized as follows:

N,N,αS-Tris(phenylmethyl)-2S-) oxiranemethanamine

^1H NMR (400 MHz, $CDCl_3$) ∂2.49 and 2.51 (AB-System, 1H, J_{AB}=2.82), 2.76 and 2.77 (AB-System, 1H, J_{AB}=4.03), 2.83 (m, 2H), 2.99 & 3.03 (AB-System, 1H, J_{AB}=10.1 Hz), 3.15 (m, 1H), 3.73 & 3.84 (AB-System, 4H, J_{AB}=14.00), 7.21 (m, 15H); ^{13}C NMR (400 MHz,$CDCl_3$) ∂139.55, 129.45, 128.42, 128.14, 128.09, 126.84, 125.97, 60.32, 54.23, 52.13, 45.99, 33.76; HRMS calcd for $C_{24}H_{26}NO$ (M+1) 344.477, found 344.2003.

N,N,αS-Tris(phenylmethyl)-2R- Oxiranemethanamine

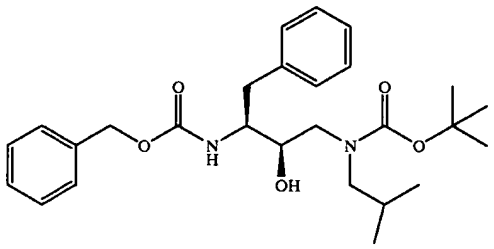
^1H NMR (300 MHz, $CDCl_3$) ∂2.20 (m, 1H), 2.59 (m, 1H), 2.75 (m, 2H), 2.97 (m, 1H), 3.14 (m, 1H), 3.85 (AB-System, 4H), 7.25 (m, 15H). HPLC on chiral stationary phase: Pirkle-Whelk-O 1 column (250×4.6 mm I.D.), mobile phase: hexane/isopropanol (99.5:0.5, v/v), flow-rate: 1.5 ml/min, detection with UV detector at 210 nm. Retention time of (8): 9.38 min., retention time of enanatiomer of (4): 13.75 min.

Alternatively, a solution of the crude aldehyde 0.074 mol and chloroiodomethane (7.0 ml, 0.096 mol) in tetrahydrofuran (285 ml) was cooled to −78° C., under a nitrogen atmosphere. A 1.6 M solution of n-butyllithium in hexane (25 ml, 0.040 mol) was then added at a rate to maintain the temperature at −75° C. (addition time−15 min.). After the first addition, additional chloroiodomethane (1.6 ml, 0.022 mol) was added again, followed by n-butyllithium (23 ml, 0.037 mol), keeping the temperature at −75° C. The mixture was stirred for 15 min. Each of the reagents, chloroiodomethane (0.70 ml, 0.010 mol) and n-butyllithium (5 ml, 0.008 mol) were added 4 more times over 45 min. at −75° C. The cooling bath was then removed and the solution warmed to 22° C. over 1.5 hr. The mixture was poured into 300 ml of saturated aq. ammonium chloride solution. The tetrahydrofuran layer was separated. The aqueous phase was extracted with ethyl acetate (1×300 ml). The combined organic layers were washed with brine, dried over magne-

sium sulfate, filtered and concentrated to give a brown oil (27.4 g). The product could be used in the next step without purification. The desired diastereomer can be purified by recrystallization at a subsequent step. The product could also be purified by chromatography.

Alternatively, a solution of αS-[Bis(phenylmethyl)amino] benzene-propanaldehyde (178.84 g, 0.54 mol) and bromochloromethane (46 mL, 0.71 mol) in tetrahydrofuran (1.8 L) was cooled to −30 to −35° C. (colder temperature such as −70° C. also worked well but warmer temperatures are more readily achieved in large scale operations) in a stainless steel reactor under a nitrogen atmosphere. A solution of n-butyllithium in hexane (1.6 M, 340 mL, 0.54 mol) was then added at a rate that maintained the temperature below −25° C. After addition the mixture was stirred at −30 to −35° C. for 10 minutes. More additions of reagents were carried out in the following manner: (1) additional bromochloromethane (14 mL) was added, followed by n-butyllithium (102 mL) at <−25° C. After addition the mixture was stirred at −30 to −35° C. for 10 minutes. This was repeated once. (2) Additional bromochloromethane (9 mL, 0.11 mol) was added, followed by n-butyllithium (51 mL, 0.082 mol) at <−25° C. After addition the mixture was stirred at −30 to −35° C. for 10 minutes. This was repeated 5 times. (3) Additional bromochloromethane (7 mL, 0.11 mol) was added, followed by n-butyllithium (51 mL, 0.082 mol) at <−25° C. After addition the mixture was stirred at −30 to −35° C. for 10 minutes. This was repeated once. The external cooling was stopped and the mixture warmed to ambient temp. over 4 to 16 hours when TLC (silica gel, 20% ethyl acetate/hexane) indicated that the reaction was completed. The reaction mixture was cooled to 10° C. and quenched with 1452 g of 16% ammonium chloride solution (prepared by dissolving 232 g of ammonium chloride in 1220 mL of water), keeping the temperature below 23° C. The mixture was stirred for 10 minutes and the organic and aqueous layers were separated. The aqueous phase was extracted with ethyl acetate (2×500 mL). The ethyl acetate layer was combined with the tetrahydrofuran layer. The combined solution was dried over magnesium sulfate (220 g), filtered and concentrated on a rotary evaporator at 65° C. The brown oil residue was dried at 70° C. in vacuo (0.8 bar) for 1 h to give 222.8 g of crude material.

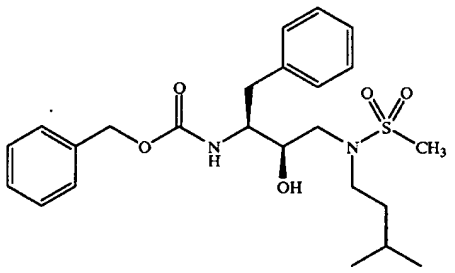
EXAMPLE 2



Preparation of N - [[3S-(phenylmethylcarbamoyl) amino]-2R-hydroxy-4-phenyl]-1-[(2-methylpropyl) amino-2-(1,1-dimethylethoxyl)carbonyl]butane

To a solution of 7.51 g (20.3 mmol) of N-[[3S-(phenylmethylcarbamoyl)amino]-2R-hydroxy-4-phenylbutyl]-N-(2-methylpropyl)]amine in 67 mL of anhydrous tetrahydrofuran was added 2.25 g (22.3 mmol) of triethylamine. After cooling to 0° C., 4.4 g (20.3 mmol) of di-tert-butyldicarbonate was added and stirring continued at room temperature for 21 hours. The volatiles were removed in vacuo, ethyl acetate added, then washed with 5% citric acid, saturated sodium bicarbonate, brine, dried over magnesium sulfate, filtered and concentrated to afford 9.6 g of crude product. Chromatography on silica gel using 30% ethyl acetate/hexane afforded 8.2 g of pure N-[[3S-(phenylmethylcarbamoyl)amino]-2R-hydroxy-4-phenyl]1-[(2-methylpropyl)amino-2-(1,1-dimethylethoxyl)carbonyl] butane, mass spectum m/e=477 (M+Li).

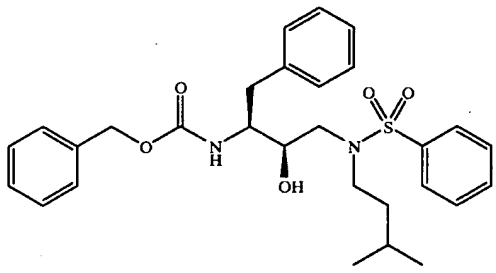
EXAMPLE 3A



Preparation of phenylmethyl[2R-hydroxy-3-[(3-methylbutyl)(methylsulfonyl)amino]-1S-(phenylmethyl)propyl]carbamate

To a solution of N[3(S)-benzyloxycarbonylamino-2(R)-hydroxy-4-phenylbutyl]N-isoamylamine (2.0 gm, 5.2 mmol) and triethylamine (723 uL, 5.5 mmol) in dichloromethane (20 mL) was added dropwise methanesulfonyl chloride (400 uL, 5.2 mmol). The reaction mixture was stirred for 2 hours at room temperature, then the dichloromethane solution was concentrated to ca. 5 mL and applied to a silica gel column (100 gm). The column was eluted with chloroform containing 1% ethanol and 1% methanol. The phenylmethyl [2R-hydroxy-3-[(3-methylbutyl)(methylsulfonyl)amino]-1S-(phenylmethyl) propyl]carbamate was obtained as a white solid Anal. Calcd for $C_{24}H_{34}N_2O_5S$: C, 62.31; H, 7.41; N, 6.06. Found: C, 62.17; H, 7.55; N, 5.97.

EXAMPLE 3B

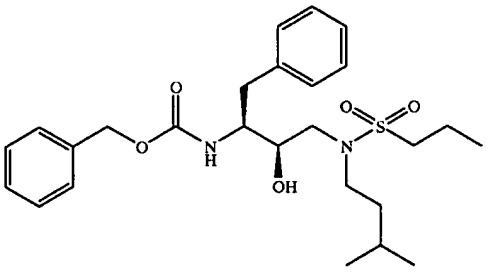


Preparation of phenylmethyl[2R-hydroxy-3-[(3-methylbutyl)(phenylsulfonyl)amino]-1S-(phenylmethyl)propyl]carbamate

From the reaction of N[3(S)-benzyloxycarbonylamino-2(R)-hydroxy-4-phenylbutyl]N-isoamylamine (1.47 gm, 3.8 mmol), triethylamine (528 uL, 3.8 mmol) and benzenesulfo-

nyl chloride (483 uL., 3.8 mmol) one obtains phenylmethyl [2R-hydroxy-3-[(3-methylbutyl)(phenylsulfonyl)amino]1S-(phenylmethyl)propyl]-carbamate. Column chromatography on silica gel eluting with chloroform containing 1% ethanol afforded the pure product. Anal. Calcd for $C_{29}H_{36}N_2O_5S$: C, 66.39; H, 6.92; N, 5.34. Found: C, 66.37; H, 6.93; N, 5.26.

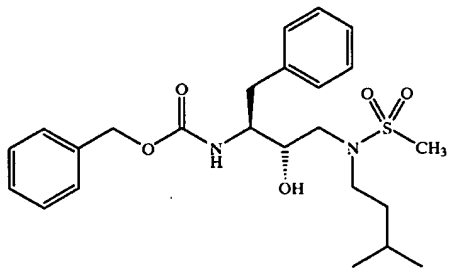
EXAMPLE 4



Preparation of Phenylmethyl[2R-hydroxy-3-[(3-methylbutyl)(n-propanesulfonyl)amino]-1S-(phenylmethyl)propyl]carbamate

To a solution of N[3(S)-benzyloxycarbonylamino-2(R)-hydroxy-4-phenylbutyl]N-isoamylamine (192 mg, 0.5 mmol) and triethylamine (139 uL, 1.0 mmol) in dichloromethane (10 mL) was added dropwise trimethylsilyl chloride (63 uL, 0.5 mmol). The reaction was allowed to stir for 1 hour at room temperature, cooled to 0° C. with an ice bath and then n-propanesulfonyl chloride (56 uL, 0.5 mmol) was added dropwise. The reaction mixture was stirred for 1.5 hours at room temperature, then diluted with ethyl acetate (50 mL) and washed sequentially with 1N HCl, water, saturated sodium bicarbonate solution, and saturated sodium chloride solution (25 mL each). The organic solution was dried over magnesium sulfate, filtered and concentrated to an oil. The oil was stirred with methanol (10 mL) for 16 hours, concentrated and the residue chromatographed on silica gel (50 gm) eluting with 10% ethyl acetate in hexane (450 mL), then with 1:1 ethyl acetate/hexane. The phenylmethyl[2R-hydroxy-3-[(3-methylbutyl)(n-propanesulfonyl)amino]-1S-(phenylmethyl)propyl] carbamate was recrystallized from ethyl ether/hexane to afford a white solid Anal. Calcd. for $C_{26}H_{38}N_2O_5S$: C, 63.64; H, 7.81; N, 5.71. Found: C, 63.09; H, 7.74; N, 5.64.

EXAMPLE 5



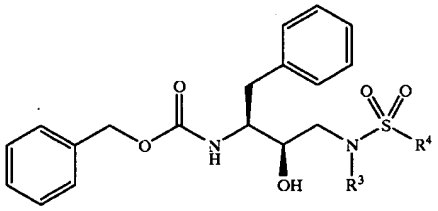
The procedure described in Example 2 was used to prepare phenylmethyl[2S-hydroxy-3-[(3-methylbutyl)(methylsulfonyl)amino]-1S-(phenylmethyl)propyl] carbamate.

To a solution of N[3(S)-benzyloxycarbonylamino-2(S)-hydroxy-4-phenylbutyl]N-isoamylamine (192 mg, 0.5 mmol) and triethylamine (139 uL, 0.55 mmol) in dichloromethane (8 mL) was added dropwise methanesulfonyl chloride (39 uL, 0.55 mmol). The reaction mixture was stirred for 16 hours at room temperature, then the dichloromethane solution was applied to a silica gel column (50 gm). The column was eluted with dichloromethane containing 2.5% methanol. The phenylmethyl [2S-hydroxy-3-[(3-methylbutyl)(methylsulfonyl)amino]-1S-(phenylmethyl) propyl]carbamate was obtained as a white solid Anal. Calcd. for $C_{24}H_{34}N_2O_5S \diamond 0.2\ H_2O$: C, 61.83; H, 7.44; N, 6.01. Found: C, 61.62; H, 7.40; N, 5.99.

EXAMPLE 6

Following the procedures of the previous Examples 1–5, the compounds set forth in Tables 1A and 1B were prepared.

TABLE 1A



Entry	R3	R4
1	isoamyl	p-fluorophenyl
2	isoamyl	p-nitrophenyl
3	isoamyl	o-nitrophenyl
4	isoamyl	β-naphthyl
5	isoamyl	2-thienyl
6	isoamyl	benzyl
7	isobutyl	p-fluorophenyl
8	p-fluorobenzyl	phenyl
9	4-pyridylmethyl	phenyl
10	cyclohexylmethyl	phenyl
11	allyl	phenyl

TABLE 1A-continued

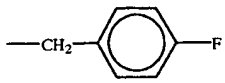
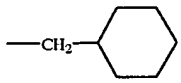
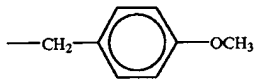
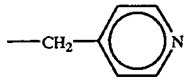
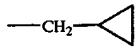
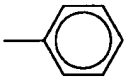
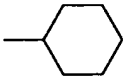
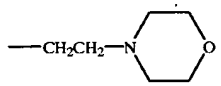
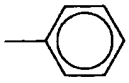
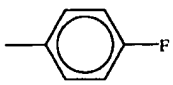
12	propyl	phenyl
13	cyclopropylmethyl	phenyl
14	methyl	phenyl
15	propargyl	phenyl
16	isoamyl	p-chlorophenyl
17	isoamyl	p-methoxyphenyl
18	isoamyl	m-nitrophenyl
19	isoamyl	m-trifluoromethylphenyl
20	isoamyl	o-methoxycarbonylphenyl
21	isoamyl	p-acetamidophenyl
22	isobutyl	phenyl
23	—CH_2Ph	—Ph
24		—Ph
25		—Ph
26		—Ph
27		—Ph
28		—Ph
29	—$CH_2CH{=}CH_2$	—Ph
30		—Ph
31		—Ph
32	—CH_2CH_2Ph	—Ph
33	—$CH_2CH_2CH_2CH_2OH$	—Ph
34	—$CH_2CH_2N(CH_3)_2$	—Ph
35		—Ph
36	—CH_3	—Ph
37	—$CH_2CH_2CH_2SCH_3$	—Ph
38	—$CH_2CH_2CH_2S(O)_2CH_3$	—Ph
39	—$CH_2CH_2CH(CH_3)_2$	
40	—$CH_2CH_2CH(CH_3)_2$	—$CH_2CH_2CH_3$
41	—$CH_2CH_2CH(CH_3)_2$	—CH_3
42	—$CH_2CH_2CH(CH_3)_2$	

TABLE 1A-continued

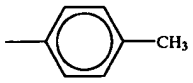
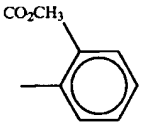
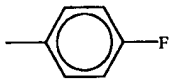
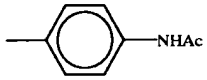
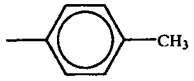
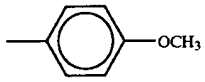
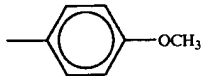
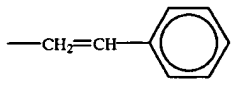
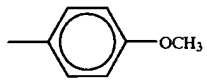
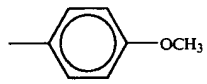
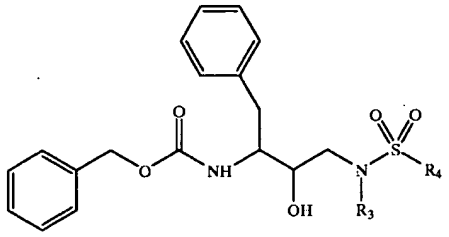
43	$-CH_2CH_2CH(CH_3)_2$	
44	$-CH_2CH_2CH(CH_3)_2$	
45	$-CH_2CH(CH_3)_2$	
46	$-CH_2CH(CH_3)_2$	
47	$-CH_2CH(CH_3)_2$	
48	$-CH_2CH_2CH_3$	
49	$-CH_2CH_2CH_2CH_3$	
50	$-CH_2CH_2CH(CH_3)_2$	$-CF_3$
51	$-CH_2CH(CH_3)_2$	$-CH_3$
52	$-CH_2CH_2CH(CH_3)_2$	$-CH_2Cl$
53	$-CH_2CH(CH_3)_2$	
54	$-CH_2CH(CH_3)_2$	
55	$-CH_2CH(CH_3)_2$	$-CH=CH_2$
56	$-CH_2-CH)CH_3)$ (CH_2CH_3)	

TABLE 1A-continued



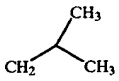
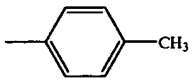
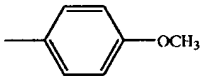
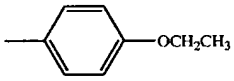
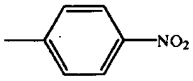
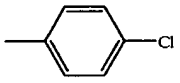
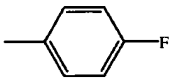
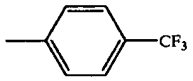
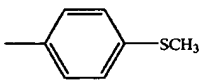
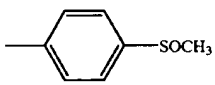
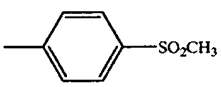
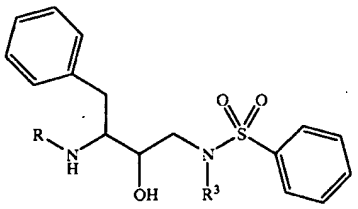
Entry	R^3	R^4	MASS MEASUREMENT MOL FORM	CALC	FOUND
1			$C_{29}H_{36}N_2O_5S$	531 (M + Li)	531
2			$C_{29}H_{36}N_2O_6S$	541(M + H)	541
3			$C_{30}H_{36}N_2O_6S$	555.2529(M + H)	555.2582
4					
5					
6			$C_{28}H_{33}N_2O_5SF$	529.2172(M + H)	521.2976
7					
8			$C_{29}H_{36}N_2O_5S_2$	563 (M + Li)	563
9			$C_{29}H_{36}N_2O_6S_2$	573(M + H)	573
10			$C_{29}H_{36}N_2O_7S_2$	595 (M + Li)	595

TABLE 1B



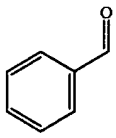
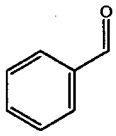
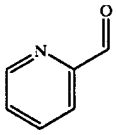
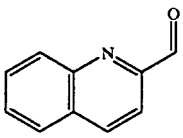
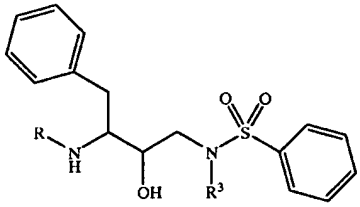
Entry	R	R_3
1		—CH_2Ph
2		$CH_2CH_2CH(CH_3)_2$
3		—$CH_2CH(CH_3)_2$
4		—$CH_2CH(CH_3)_2$
5		—$CH_2CH(CH_3)_2$

TABLE 1B-continued



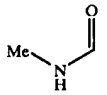
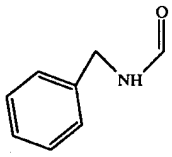
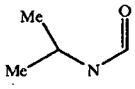
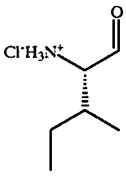
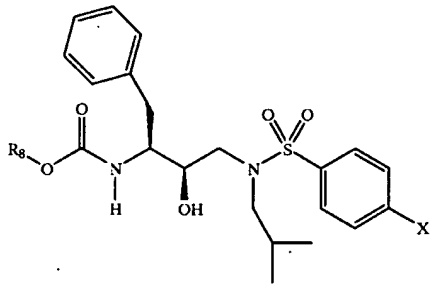
Entry	R	R_3
6		—$CH_2CH(CH_3)_2$
7		—$CH_2CH(CH_3)_2$
8		—$CH_2CH(CH_3)_2$
9		—$CH_2CH_2(CH_3)_2$

TABLE 1C



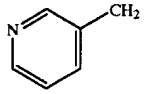
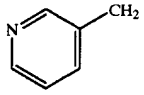
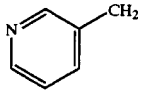
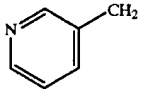
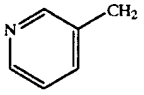
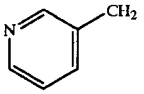
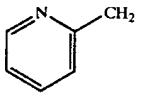
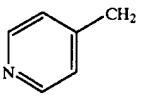
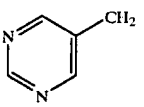
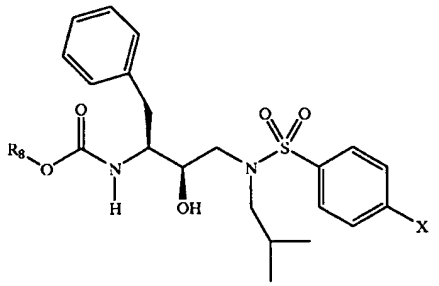
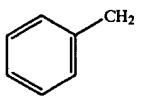
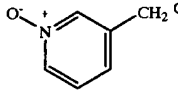
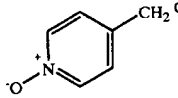
X	R^8	FORMULA	Mass Determination Calc	Found
H		$C_{27}H_{33}N_3O_5S$	512:2219(M + H)	521.2267
OCH_3		$C_{28}H_{35}N_3O_6S$	548.2407(M + Li)	548.2434
F		$C_{27}H_{32}N_3O_5SF$	530(M + H)	530
Cl		$C_{27}H_{32}N_3O_5SCl$	546(M + H)	546
NO_2		$C_{27}H_{32}N_4O_7S$	557(M + H)	557
OH		$C_{27}H_{33}N_3O_6S$	528(M + H)	528
OCH_3		$C_{28}H_{35}N_3O_6S$	542.2325(M + H)	542.2362
OCH_3		$C_{28}H_{35}N_3O_6S$	548.2407(M + Li)	548.2393
OCH_3		$C_{28}H_{35}N_3O_6S$	543(M + H)	543

TABLE 1C-continued

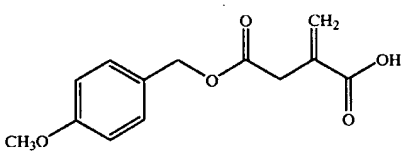


X	R^8	FORMULA	Mass Determination Calc	Found
OCH_3		$C_{29}H_{36}O_6N_2S$	547.2454(M + Li)	547.2475
OCH_3	tert-Butyl	$C_{26}H_{38}N_2O_6S$	513.2611(M + Li)	513.2593
OCH_3		$C_{28}H_{35}N_3O_7S$	564(M + Li)	564
OCH_3		$C_{28}H_{35}N_3O_7S$	564(M + Li)	564

The following Examples 7–9 illustrate preparation of β-amino acid intermediates. These intermediates can be coupled to the intermediate compounds of Examples 1–6 to produce inhibitor compounds of the present invention containing β-amino acids.

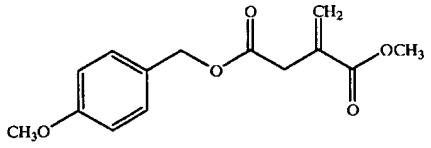
EXAMPLE 7

A. Preparation of 4(4-methoxybenzyl)itaconate



A 5 L three-necked round bottomed flask equipped with constant pressure addition funnel, reflux condenser, nitrogen inlet, and mechanical stirrer was charged with itaconic anhydride (660.8 g, 5.88 mol) and toluene (2300 mL). The solution was warmed to reflux and treated with 4-methoxybenzyl alcohol (812.4 g, 5.88 mol) dropwise over a 2.6 h period. The solution was maintained at reflux for an additional 1.5 h and then the contents were poured into three 2 L erlenmeyer flasks to crystallize. The solution was allowed to cool to room temperature whereupon the desired mono-ester crystallized. The product was isolated by filtration on a Buchner funnel and air dried to give 850.2 g, 58% of material with mp 83–85° C., a second crop, 17% was isolated after cooling of the filtrate in an ice bath. ^1H NMR ($CDCl_3$) 300 MHz 7.32(d, J=8.7 Hz, 2H), 6.91(d, J=8.7 Hz, 2H), 6.49(s, 1H), 5.85(s, 1H), 5.12(s, 2H), 3.83(s, 3H), 3.40(s, 2H).

B. Preparation of Methyl 4(4-methoxybenzyl) itaconate

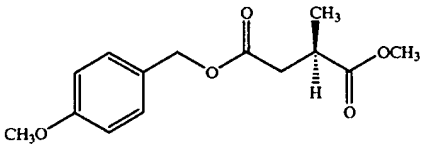


A 5 L three-necked round bottomed flask equipped with reflux condenser, nitrogen inlet, constant pressure addition funnel and mechanical stirrer was charged with 4(4-methoxybenzyl)itaconate (453.4 g, 1.81 mol) and treated with 1,5-diazabicyclo[4.3.0]non-5-ene (275.6 g, 1.81 mol), (DBN), dropwise so that the temperature did not rise above 15° C. To this stirring mixture was added a solution of methyl iodide (256.9 g, 1.81 mol) in 250 mL of toluene from the dropping funnel over a 45 m period. The solution was allowed to warm to room temperature and stirred for an additional 3.25 h.

The precipitated DBN hydroiodide was removed by filtration, washed with toluene and the filtrate poured into a

separatory funnel. The solution was washed with sat. aq. $NaHCO_3$ (2×500 mL), 0.2N HCl (1×500 mL), and brine (2×500 mL), dried over anhyd. $MgSO_4$, filtered, and the solvent removed in vacuo. This gave a clear colorless oil, 450.2 g, 94% whose NMR was consistent with the assigned structure. ^1H NMR ($CDCl_3$) 300 MHz 7.30(d, J=8.7 Hz, 2H), 6.90(d, J=8.7 Hz, 2H), 6.34(s, 1H), 5.71(s, 1H), 5.09(s, 2H), 3.82(s, 3H), 3.73(s, 3H), 3.38(s, 2H). ^{13}C NMR ($CDCl_3$) 170.46, 166.47, 159.51, 133.55, 129.97, 128.45, 127.72, 113.77, 66.36, 55.12, 51.94, 37.64.

C. Preparation of Methyl 4(4-methoxybenzyl)2(R)-methylsuccinate

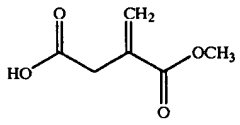


A 500 mL Fisher-Porter bottle was charged with methyl 4(4-methoxybenzyl) itaconate (71.1 g, 0.269 mol), rhodium (R,R) DiPAMP catalyst (204 mg, 0.269 mmol, 0.1 mol %) and degassed methanol (215 mL). The bottle was flushed 5 times with nitrogen and 5 times with hydrogen to a final pressure of 40 psig. The hydrogenation commenced immediately and after ca. 1h the uptake began to taper off, after 3 h the hydrogen uptake ceased and the bottle was flushed with nitrogen, opened and the contents concentrated on a rotary evaporator to give a brown oil that was taken up in boiling iso-octane (ca. 200 mL, this was repeated twice), filtered through a pad of celite and the filtrate concentrated in vacuo to give 66.6 g, 93% of a clear colorless oil, ^1H NMR ($CDCl_3$ MHz 7.30(d, J=8.7 Hz, 2H), 6.91(d, J=8.7 Hz, 2H), 5.08(s, 2H), 3.82(s, 3H), 3.67(s, 3H), 2.95(ddq, J=5.7, 7.5, 8.7 Hz, 1H), 2.79(dd, J=8.1, 16.5 Hz, 1H), 2.45(dd, J=5.7, 16.5 Hz, 1H), 1.23(d, J=7.5 Hz, 3H).

D. Preparation of Methyl 2(R)-methylsuccinate

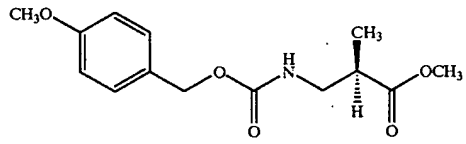
A 3 L three-necked round-bottomed flask equipped with a nitrogen inlet, mechanical stirrer, reflux condenser and constant pressure addition funnel was charged with methyl 4(4-methoxybenzyl) 2(R)-methylsuccinate (432.6 g, 1.65 mol) and toluene (1200 mL). The stirrer was started and the solution treated with trifluoroacetic acid (600 mL) from the dropping funnel over 0.25 h. The solution turned a deep purple color and the internal temperature rose to 45° C. After stirring for 2.25 h the temperature was 27° C. and the solution had acquired a pink color. The solution was concentrated on a rotary evaporator. The residue was diluted with water (2200 mL) and sat. aq. $NaHCO_3$ (1000 mL). Additional $NaHCO_3$ was added until the acid had been neutralized. The aqueous phase was extracted with ethyl acetate (2×1000 mL) to remove the by-products and the aqueous layer was acidified to pH=1.8 with conc. HCl. This solution was extracted with ethyl acetate (4×1000 mL), washed with brine, dried over anhyd. $MgSO_4$, filtered and concentrated on a rotary evaporator to give a colorless liquid 251 g, >100% that was vacuum distilled through a short path apparatus cut 1: bath temperature 120° C. @ >1 mm, bp 25–29° C.; cut 2: bath temperature 140° C. @ 0.5 mm, bp 95–108° C., 151 g, $[\alpha]_d$ @ 25° C.=+1.38° C.(c=15.475, MeOH), $[\alpha]_d$=+8.48° C. (neat); cut 3: bath temperature 140° C., bp 108° C., 36 g, $[\alpha]_d$ @ 25° C.=+1.49° C.(c=15.00, MeOH), $[\alpha]_d$=+8.98° C. (neat). Cuts 2 and 3 were combined to give 189 g, 78% of product, ^1H NMR ($CDCl_3$) 300 MHz 11.6(brs, 1H), 3.72(s, 3H), 2.92(ddq, J=5.7, 6.9, 8.0 Hz, 1H), 2.81(dd, J=8.0, 16.8 Hz, 1H), 2.47(dd, J=5.7, 16.8 Hz, 1H), 1.26(d, J=6.9 Hz, 3H).

E. Preparation of Methyl Itaconate



A 50 mL round bottomed flask equipped with reflux condenser, nitrogen inlet and magnetic stir bar was charged with methyl 4(4-methoxybenzyl) itaconate (4.00 g, 16 mmol), 12 mL of touluene and 6 mL of trifluoroacetic acid. The solution was kept at room temperature for 18 hours and then the volatiles were removed in vacuo. The residue was taken up in ethyl acetate and extracted three times with saturated aqueous sodium bicarbonate solution. The combined aqueous extract was acidified to pH=1 with aqueous potassium bisulfate and then extracted three times with ethyl acetate. The combined ethyl acetate solution was washed with saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue was then vacuum distilled to give 1.23 g, 75% of pure product, bp 85–87 @ 0.1 mm. ^1H NMR ($CDCl_3$) 300 MHz 6.34(s, 1H), 5.73(s, 2H), 3.76(s, 3H), 3.38(s, 2H). ^{13}C NMR ($CDCl_3$) 177.03, 166.65, 129.220, 132.99, 52.27, 37.46.

F. Curtius Rearrangement of Methyl 2(R)-methylsuccinate: Preparation of Methyl N-Moz-α-methyl β-alanine

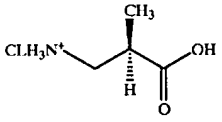


A 5 L four necked round bottomed flask equipped with a nitrogen inlet, reflux condenser, mechanical stirrer, constant pressure addition funnel, and thermometer adapter was charged with methyl 2(R)-methylsuccinate (184.1 g, 1.26 mol), triethylamine (165.6 g, 218 mL, 1.64 mol, 1.3 equivalents), and toluene (1063 mL). The solution was warmed to 85° C. and then treated dropwise with a solution of diphenylphosphoryl azide (346.8 g, 1.26 mol) over a period of 1.2 h. The solution was maintained at that temperature for an additional 10 h and then the mixture was treated with 4-methoxybenzyl alcohol (174.1 g, 1.26 mol) over a 0.33 h period from the dropping funnel. The solution was stirred at 88° C. for an additional 2.25 h and then cooled to room temperature. The contents of the flask were poured into a separatory funnel and washed with sat. aq. $NaHCO_3$

(2×500 mL), 0.2N HCl (2×500 mL), brine (1×500 mL), dried over anhyd. $MgSO_4$, filtered, and concentrated in vacuo to give 302.3 g, 85% of the desired product as a slightly brown oil. $_1$H NMR ($CDCl_3$) 300 MHz 7.32(d, J=8.4 Hz, 2H), 6.91(d, J=8.4 Hz, 2H), 5.2(brm, 1H), 5.05(s, 2H), 3.83(s, 3H), 3.70(s, 3H), 3.35(m, 2H), 2.70(m, 2H), 1.20(d, J=7.2 Hz, 3H).

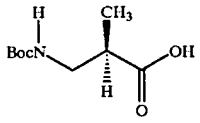
G. Hydrolysis of Methyl N-Moz-α-methyl β-alanine:

Preparation of α-methyl β-alanine Hydrochloride



A 5 L three-necked round bottomed flask equipped with a reflux condenser, nitrogen inlet and mechanical stirrer was charged with methyl N-Moz-α-methyl β-alanine (218.6 g, 0.78 mol), glacial acetic acid (975 mL) and 12N hydrochloric acid (1960 mL). The solution was then heated to reflux for 3 h. After the solution had cooled to room temperature (ca. 1 h) the aqueous phase was decanted from organic residue (polymer) and the aqueous phase concentrated on a rotary evaporator. Upon addition of acetone to the concentrated residue a slightly yellow solid formed that was slurried with acetone and the white solid was isolated by filtration on a Buchner funnel. The last traces of acetone were removed by evacuation to give 97.7 g, 90% of pure product, mp 128.5–130.5° C. $[\alpha]_d$ @ 25° C.=9.0° C. (c=2.535, Methanol). ^{1}H NMR (D_2O) 300 MHz 3.29(dd, J=8.6, 13.0 Hz, 1H), 3.16(dd, J=5.0, 13.0m Hz, 1H), 2.94 (ddq, J=7.2, 5.0, 8.6 Hz, 1H), 1.30(d,J=7.2 Hz, 3H); ^{13}C NMR (D_2O) 180.84, 44.56, 40.27, 17.49.

H. Preparation of N-Boc α-Methyl β-Alanine



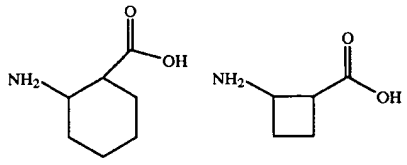
A solution of a-methyl b-alanine hydrochloride (97.7 g, 0.70 mol) in water (1050 mL) and dioxane (1050 mL) the pH was adjusted to 8.9 with 2.9N NaOH solution. This stirring solution was then treated with di-tert-butyl pyrocarbonate (183.3 g, 0.84 mol, 1.2 equivalents) all at once. The pH of the solution was maintained between 8.7 and 9.0 by the periodic addition of 2.5N NaOH solution. After 2.5 h the pH had stabilized and the reaction was judged to be complete. The solution was concentrated on a rotary evaporator (the temperature was maintained at <40° C.). The excess di-tert-butyl pyrocarbonate was removed by extraction with dichloromethane and then the aqueous solution was acidified with cold 1N HCl and immediately extracted with ethyl acetate (4×1000 mL). The combined ethyl acetate extract was washed with brine, dried over anhyd. $MgSO_4$, filtered and concentrated on a rotary evaporator to give a thick oil 127.3 g, 90% crude yield that was stirred with n-hexane whereupon crystals of pure product formed, 95.65 g, 67%, mp 76–78° C., $[\alpha]_d$ @ 25° C.=−11.8° C. (C=2.4, EtOH). A second crop was obtained by concentration of the filtrate and dilution with hexane, 15.4 g, for a combined yield of 111.05 g, 78%. ^{1}H NMR (acetone D_6) 300 MHz 11.7 (brs, 1H), 6.05 (brs 1H), 3.35 (m, 1H), 3.22 (m, 1H), 2.50 (m, 1H), 1.45(s, 9H), 1.19 (d, J=7.3 Hz, 3H); ^{13}C NMR (acetone D_6) 177.01, 79.28, 44.44, 40.92, 29.08, 15.50. Elemental analysis calc'd. for $C_9H_{17}NO_4$: C, 53.19, H, 8.42; N, 6.89. Found: C, 53.36; H, 8.46; N, 6.99.

I. Preparation of N-4-Methoxybenzyloxycarbonyl α-Methyl β-Alanine

A solution of N-4-methoxybenzyloxycarbonyl α-methyl β-alanine methyl ester (2.81 g, 10.0 mmol) in 30 mL of 25% aqueous methanol was treated with lithium hydroxide (1.3 equivalents) at room temperature for a period of 2 h. The solution was concentrated in vacuo and the residue taken up in a mixture of water and ether and the phases separated and the organic phase discarded. The aqueous phase was acidified with aqueous potassium hydrogen sulfate to pH=1.5 and then extracted three times with ether. The combined ethereal phase was washed with saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo to give 2.60 g, 97% of N-4-Methoxybenzyloxycarbonyl α-methyl β-alanine (N-Moz-AMBA) which was purified by recrystallization from a mixture of ethyl acetate and hexane to give 2.44 g, 91% of pure product, mp 96–97° C., MH+=268. ^{1}H NMR (D_6-acetone/300 MHz) 1.16 (3H, d, J=7.2 Hz), 2.70 (1H, m), 3.31 (2H, m), 3.31 (3H, s), 4.99 (2H, s), 6.92 (2H, 4, J=8.7 Hz), 7.13 (2H, d, J=8.7 Hz).

EXAMPLE 8

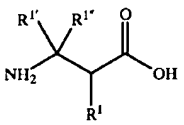
Utilizing generally the procedure set forth in Example 7, the following β-amino acid compounds were prepared.

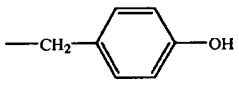
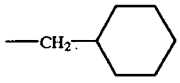
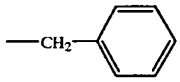
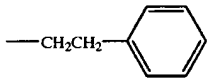
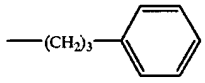
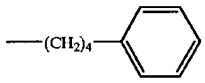


EXAMPLE 9

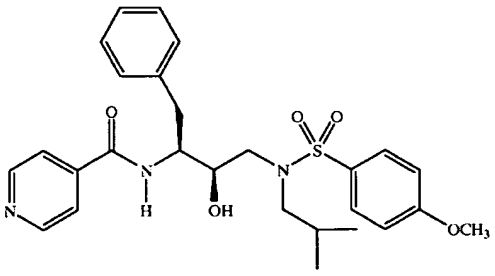
Following generally the procedure of Example 7, the β-amino acids set forth in Table 2 were prepared.

TABLE 2



Entry	R^1	$R^{1'}$	$R^{1''}$
1	$-CH_3$	H	H
2	$-CH(CH_3)_2$	H	H
3	$-C(CH_3)3$	H	H
4	H	H	H
5	H	$-CH_3$	H
6	H	$-CH_3$	$-CH_3$
7	H	H	$-CO2CH_3$
8	H	H	$-CONH_2$
9	$-CH_2CH_3$	H	H
10	$-CH_2CH(CH_3)_2$	H	H
11	$-CH_2C_6H_5$	H	H
12		H	H
13		H	H
14	$-CH_2COOH$	H	H
15	H	$-CH(CH_3)_2$	H
16	H	$-CH_2CH(CH_3)_2$	H
17	H		H
18	H		H
19	H		H
20	H		H
21	H	$-(CH_2)_3CH(C_6H_5)_2$	H

EXAMPLE 10A

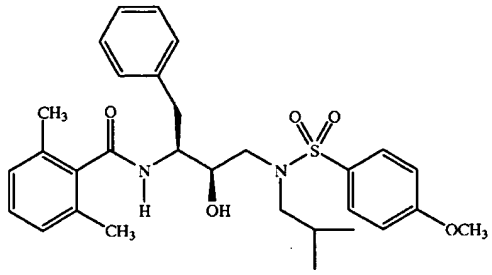


Preparation of 4-Pyridinecarboxamide, N-[2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]

To a solution of 231 mg (0.57 mmol) of 2R-hydroxy-3-[(2-methylpropyl)(4-methoxyphenyl)sulfonyl]amino-1S-(phenylmethyl)propylamine in 3 mL of methylene chloride at 0 C., was added 288 mg (2.85 mmol) of triethylamine and then 112 mg (0.63 mmol) of isonicotinoyl chloride hydrochloride. After 19 hours at room temperature, the solvent was removed, ethyl acetate added, then washed with saturated sodium bicarbonate, brine, dried with magnesium sulfate, filtered and concentrated to afford 290 mg of crude product. This was chromatographed on silica gel using 3–5% isopropanol/methylene chloride as eluent to afford

190 mg of the desired compound; mass spectrum calc. for $C_{27}H_{34}N_3O_5S$ (M+H) 512.2219;found 512.2280.

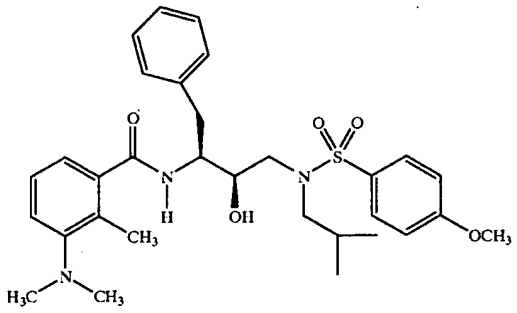
EXAMPLE 10B



Preparation of Benzamide, N-[2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-2,6-dimethyl

To a solution of 83 mg (0.55 mmol) of 2,6-dimethylbenzoic acid and 125 mg (0.82 mmol) of N-hydroxybenzotriazole in 3 mL of anhydrous DMF at 0 C. was added 117 mg (0.61 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride. After 2 hours at 0 C., 203 mg (0.50 mmol) of 2R-hydroxy-3-[(2-methylpropyl)(4-methoxyphenyl)sulfonyl]amino-1S-(phenylmethyl)propylamine was added. After 22 hours at room temperature, the solvent was removed in vacuo, ethyl acetate added, then washed with saturated sodium bicarbonate, brine, dried over magnesium sulfate, filtered and concentrated to afford 300 mg of crude product. Chromatography on silica gel using 20–50% ethyl acetate/hexane afforded 37 mg of the desired product; mass spectrum calcd for $C_{30}H_{38}N_2O_5S$ (M+H) 539.2580; found 539.2632.

EXAMPLE 10C



Preparation of Benzamide, N-[2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-2-methyl

Part A. Preparation of 4-Nitro-2-methylbenzoic Acid

A mixture of 1.0 g (3.8 mmol) of 2-iodo-nitrotoluene, 2.1 g (15.2 nmol) potassium carbonate and 27 mg (0.038 mmol) of palladium(II) dichloride bis(triphenylphosphine) in a mixture of 5 mL of water and 10 mL of N,N-dimethylformamide. This was placed in a Fisher/Porter bottle under 15 psig of carbon monoxideand heated at 70° C. for 16 hours. The solution became homogeneous when heated. The reaction was cooled, diethyl ether and water was added, the organic layer separated and discarded. The aqueous layer was acidified with 1N hydrohloric acid, extracted with ethyl acetate, washed with water, brine, dried over magnesium sulfate, filtered and concentrated to yield 0.5 g of crude material. This dissolved in ethyl acetate, hexane added and the resulting brown solid discarded. The filtrate was concentrated, and then recrystallized fom diethyl ether/hexane to afford 215 mg of 4-nitro-2-methylbenzoic acid, m/e=182(M+H).

Part B. Preparation of Benzamide, N-[2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl) amino]-1S-(phenylmethyl)propyl]-2-methyl-4-nitro

To a solution of 181 mg (1.0 mmol) of 4-nitro-2-methylbenzoic acid and 230 mg (1.5 mmol) N-hydroxybenzotriazole in 3 mL of anhydrous N,N-dimethylformamide at 0° C., was added 211 mg (1.1 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride. After stirring at 0 C. for 1 hour, 406 mg (1 mmol) of 2R-hydroxy-3-[(2-methylpropyl) (4-methoxyphenyl) sulfonyl]amino-1S-(phenylmethyl)propylamine was added. After 17 hours at room temperature, the solvent was removed under reduced pressure, ethyl acetate added, washed with 5% citric acid, saturated sodium bicarbonate, brine, dried with magnesium sulfate, filtered and concentrated to yield 0.55 g of crude product. This was chromatographed on silica gel using 20–50% ethyl acetate/hexane as eluent to afford 0.49 g of the desired benzamide, N-[2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl] amino)-1S-(phenylmethyl)propyl]-2-methyl-4-nitro, m/e=570(M+H).

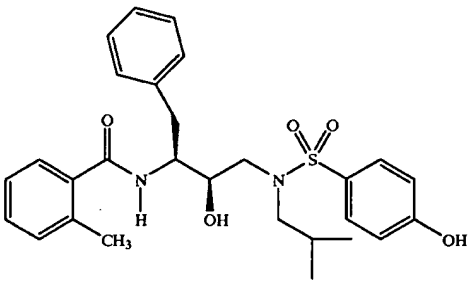
Part C. Preparation of Benzamide, N-[2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl) amino]-1S-(phenylmethyl)propyl]-2-methyl-4-amino

A solution of 400 mg (0.70 mmol) of benzamide, N-[2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl) amino]-1S-(phenylmethyl)propyl]-2-methyl-4-nitro from part B in 20 mL of methanol was hydrogenated over 0.2 g of 10% palladium on carbon catalyst under 50 psig of hydrogen for 2.5 hours. The catalyst was removed by filtration and the solution concentrated to afford 370 mg of the desired benzamide, N-[2R-hydroxy-3[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-2-methyl-4-amino, m/e=540(M+H).

Part D. Preparation of Benzamide, N-[2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl) amino]-1S-(phenylmethyl)propyl]-2-methyl-4-dimethylamino

A solution of 0.17 g (0.31 mmol) of benzamide, N-[2R-hydroxy--3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl) amino]-1S-(phenylmethyl)propyl]-2-methyl-4-amino from part C in 5 mL of methanol and 0.20 mL of 37% aqueous formaldehyde was hydrogenated over 90 mg of 10% palladium on carbon under 15 psig of hydrogen for 16 hours. The catalyst was removed by filtration, the solvents removed under reduced pressure to afford 0.16 g of crude material. Chromatography on silica gel using 50% ethyl acetate as eluent afforded 0.12 g of the desired benzamide, N-[2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl) amino]-1S-(phenylmethyl)propyl]-2-methyl-4-dimethylamino, m/e=568(M+H).

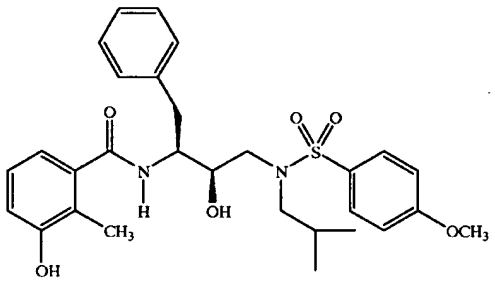
EXAMPLE 10D



Preparation of Benzamide, N-[2R-hydroxy-3-[[(4-hydroxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-2-methyl

To a solution of 500 mg (1 mmol) of 2R-hydroxy-3-[(2-methylpropyl)(4-hydroxyphenyl)sulfonyl]amino-1S-(phenylmethyl)propylamine in 2 mL of methylene chloride and 2 mL of N,N-dimethylformamide, was added 0.42 mL of triethylamine, followed by 0.12 mL of ortho-toluoyl chloride. After 17 hours, the solvent was removed under reduced pressure, the residue dissolved in ethyl acetate, was with 5% citric acid, saturated sodium bicarbonate and brine, dried over anhydrous magnesium sulfate, filtered and concentrated to afford 490 mg of crude material. This was chromatographed over 100 g of silica gel using 20–50% ethyl acetate/hexane as eluent to afford 232 mg of the desired product, m/e=511 (M+H).

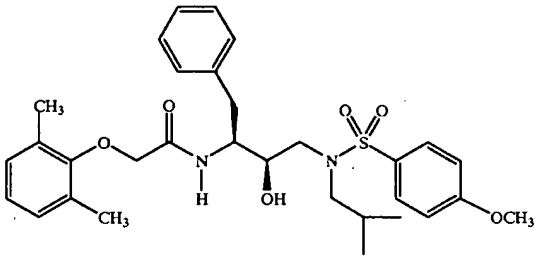
EXAMPLE 10E



Preparation of Benzamide, N-[2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-3-hydroxy-2-methyl

To a solution of 131 mg (0.86 mmol) of 3-hydroxy-2-methylbenzoic acid and 305 mg (0.75 mmol) of N-hydroxybenzotriazole in 4 mL of anhydrous N,N-dimethylformamide at 0° C., was added 165 mg (0.86 mmol) of EDC. After 20 minutes of activation at 0° C. and 1 hour at room temperature, 305 mg (0.75 mmol) of 2R-hydroxy-3-[(2-methylpropyl)(4-methoxyphenyl)sulfonyl]amino-1S-(phenylmethyl)propylamine was added. After 15 hours at room temperature, ethyl acetate was added, washed with 5% citric acid, saturated sodium bicarbonate, brine, dried, filtered and concentrated to afford 460 mg of crude material. This was chromatographed on silica gel using 0–35% ethyl acetate/methylene chloride as eluent to afford 250 mg of pure benzamide, N-[2R-hydroxy-3-[[(4-methoxyphenyl) sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl) propyl]-3-hydroxy-2-methyl, m/e=547 (M+Li).

EXAMPLE 10F



Preparation of N-[2R-hydroxy-3-[[(4-methoxyphenyl) sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-(2,6-dimethylphenoxy) acetamide

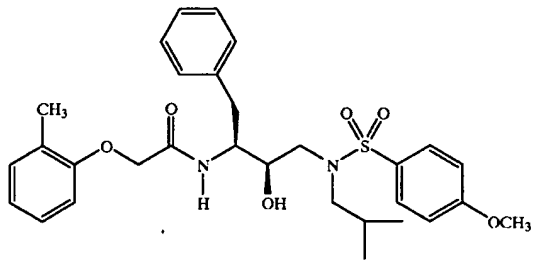
Part A: Preparation of 2,6-Dimethylphenoxyacetic acid

2,6-Dimethylphenol (6.1 g, 50.0 mmol), bromoacetic acid (6.9 g, 50.0 mol) and 2.5 N aqueous sodium hyroxide (50.0 mL, 125.0 mmol) were refluxed in water (125 mL) for 4 hrs. Bromoacetic acid (6.9 g, 50.0 mmol) and 2.5 N aqueous sodium hydroxide (20.0 mL, 62.5 mmol) were added and the solution refluxed for an additional 16 hrs. The solution was cooled to room temperature and water (200 mL) was added. The pH of the solution was adjusted to 1.0 with concentrated aqueous hydrochloric acid. The resulting precipitate was collected and recrystallized from ethyl acetate/hexanes (1:9, 700 mL). 2,6-Dimethylphenoxyacetic acid (4.53 g, 25.1 mmol, 50%) was collected as a white crystalline solid. ^{1}H NMR (CD_3OD) d 2.26 (s, 6H), 4.38 (s, 2H), 6.90–7.00 (m, 3H).

Part B: Preparation of N-[2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-(2,6-dimethylphenoxy) acetamide

To a solution of 180.1 mg (0.83 mmol) of 2,6-(dimethylphenoxy)acetic acid in 10 mL of anhydrous methylene chloride at room temperature, was added 114 mg (0.60 mmol) of EDC. After 15 minutes of activation, 203 mg of 2R-hydroxy-3-[[(2-methylpropyl)(4-methoxybenzene) sulfonyl]amino]-1S-(phenylmethyl)propylamine was added. After stirring at room temperature for 16 hours the solution was extracted with 5% citric acid, sodium bicarbonate, brine, dried over magnesium sulfate, filtered and concentrated to afford 244 mg of crude product. A quantity of this (15 mg) was chromatographed on silica gel using 25% ethyl acetate/hexane to afford 8 mg of the desired compound, m/e=575(M+Li).

EXAMPLE 10G



Preparation of N-[2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-(2-methylphenoxy) acetamide

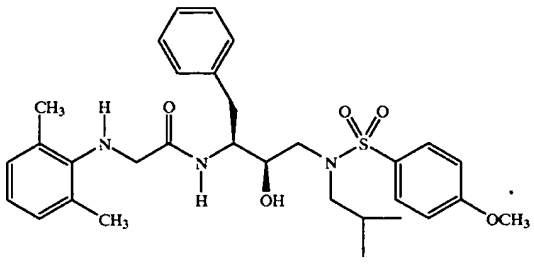
Part A: Preparation of 2-Methylphenoxyacetic Acid

2-Methylphenol (2.0 g, 18.4 mmol), bromoacetic acid (2.5 g, 18.4 mmol) and 2.5 N aqueous sodium hyroxide (25.0 mL, 62.55.0 mmol) refluxed for 16 hrs. The pH of the solution was adjusted to 1 with concentrated aqueous hydrochloric acid. The resulting precipitate was collected triturated with hexanes. The 2-methylphenoxyacetic acid (720 mg, 4.33 mmol, 25%) was collected as a white crystalline solid. 1HNMR (CD_3OD) d 2.43 (s, 3H), 4.65 (s, 2H) 6.70–7.10 (m, 4H).

Part B: Preparation of N-[2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-(2-methylphenoxy) acetamide

To a solution of 97 mg (0.59 mmol) of 2-(methylphenoxy) acetic acid in 5 mL of anhydrous methylene chloride at room temperature, was added 89.1 mg (0.55 mmol) of carbonyl diimidazole. After 15 minutes of activation, 200 mg (0.49 mmol) of ^{2}R-hydroxy-3-[[(2-methylpropyl)(4-methoxybenzene)sulfonyl]amino]-1S-(phenylmethyl) propylamine was added. After stirring at room temperature for 15 hours the solution was extracted with 5% citric acid, sodium bicarbonate, brine, dried over magnesium sulfate, filtered and concentrated to afford crude product. This was chromatographed on silica gel using 25% ethyl acetate/hexane to afford 198 mg of the desired compound.

EXAMPLE 10H



Preparation of N-[2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-2-(2,6-dimethylphenylamino)acetamide

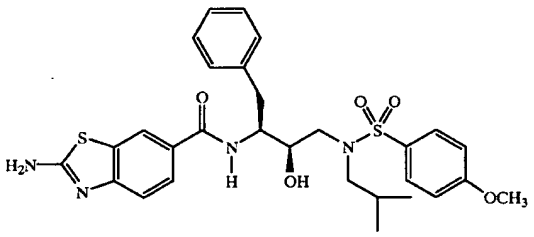
Part A: Preparation of N-(2,6Dimethylphenyl) glycine

2,6-Dimethylaniline (6.1 g, 50.4 mmol), and ethyl bromoacetate (8.4 g, 50.4 mmol) were refluxed neat for 10 min. The reaction mixture was cooled to room temperature and poured into dichloromethane (75 mL). A precipitated formed which was collected and triturated with dichloromethane (25 mL). N-(2,6-Dimethylphenyl)glycine hydrobromide salt (1.21 g, 4.6 mmol, 9.0%) was collected as a white crystalline solid. ^{1}H NMR (CD3OD) d 2.48 (s, 6H), 4.29 (s, 2H), 7.00–7.10 (m, 3H).

Part B: Preparation of N-[2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-2-(2,6-dimethylphenylamino)acetamide

To a solution of 100 mg (0.39 mmol) of N-(2,6-dimethylphenyl)glycine hydrobromide and 100 mg of triethylamine in 5 mL of anhydrous methylene chloride at room temperature, was added 74 mg (0.39 mmol) of EDC. After 15 minutes of activation, 157 mg (0.39 mmol) of 2R-hydroxy-3-[[(2-methylpropyl)(4-methoxybenzene) sulfonyl]amino]-1S-(phenylmethyl)propylamine was added. After stirring at room temperature for 4 hours, an additional 100 mg of N-(2,6-dimethylphenyl)glycine and 74 mg of EDC was added. After stirring at room temperature for 16 hours, the solution was extracted with 5% citric acid, sodium bicarbonate, brine, dried over magnesium sulfate, filtered and concentrated to afford 206 mg of crude product. This was purified by chromtaogragphy on reverse phase using 20–90% acetonitrile/water (0.05% trifluoroacetic acid) to afford 75 mg of the desired compound, m/e=568 (M+H).

EXAMPLE 10I



Preparation of N-[2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-2-amino-benzothiazole-6-carboxamide

Part A: Preparation of 2-Amino-6-Carboxy-Benzothiazole Ethyl Ester

A 100 ml round bottom flask equipped with magnetic stir bar and N_2 inlet was charged with 1.0 g of methyl p-aminobenzoate in 35 mL methanol. The solution was heated to reflux and 4.0 g of $Cu^{II}SO_4$ and 5.0 g of KSCN were added. The reaction mixture was refluxed 2 hours and then filtered. The filtrate was diluted with 60 mL of water and 20 mL of ethanol and heated to boiling. Upon cooling 1.15 g (78%) of 2-Amino-6-Carboxy-Benzothiazole Ethyl Ester was isolated, m/e=223 (M+H).

Part B: Preparation of 2-Amino-6-Carboxy-Benzothiazole

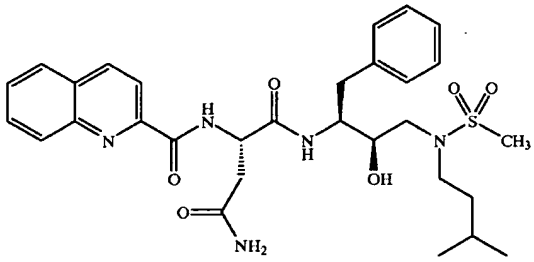
A 50 mL round bottom flask equipped with magnetic stir bar was charged with 250 mg 2-Amino-6-Carboxy-Benzothiazole Ethyl Ester, 190 mg (4 eq.) LiOH in 3 mL dioxane and 3 mL water. The slurry was heated to 60° C. for

2 hours. After 2 hours the solution was acidified with 1N HCl and concentrated in vacuo to a light grey solid which was identified as 2-amino-6-carboxy-benzothiazole, m/e= 195(M+H). It was used without further purification.

Part C: Preparation of N-[2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-2-amino-benzothiazole-6-carboxamide

A 100 mL round bottom flask equipped with magnetic stir bar and N_2 inlet was charged with 110 mg 2-amino-6-carboxybenzothiazole, 110 mg EDC, and 100 mg HOBt in 4 mL dry DMF. After 30 minutes activation 203 mg amine (A) and 0.5 mL of triethylamine were added and the reaction was stirred overnight. The reaction was partioned between ethyl acetate and saturated aqueous sodium bicarbonate. The combined organics were washed with 10% aqueous Citric Aacid, water, saturated aqueous sodium bicarbonate, brine and concentrated in vacuo to 210 mg white foam, idenitifed as the desired product, m/e=589(M+Li)

EXAMPLE 11A



Preparation of N1-[2R-hydroxy-3-[(3-methylbutyl)(methyl-sulfonyl)amino]-1S-(phenylmethyl)propyl] 2S-[(2-quinolinylcarbonyl)amino]butanediamide

Part A

A solution of phenylmethyl[2R-hydroxy-3-[(3-methylbutyl)(methylsulfonyl)amino]-1S-(phenylmethyl)-propyl]carbamate prepared as in Example 3 (100 mg) in methanol (10 mL) was hydrogenated over 10% palladium on carbon for 2 hours, filtered through diatomaceous earth and concentrated to give the product as an oil.

Part B

A solution of N-CBZ-L-asparagine (61 mg, 0.23 mmol) and N-hydroxybenzotriazole (33 mg, 0.22 mmol) in DMF (2 mL) was cooled to 0° C. with an ice bath and then EDC (42 mg, 0.22 mmol) was added. The solution was stirred for 30 minutes at 0° C. and then the product of Part A (69 mg, 0.21 mmol) in DMF (2 mL) was added. After 30 minutes at 0° C. the reaction was allowed to warm to room temperature and stir for 16 hours. The reaction mixture was then poured into a 50% saturated aqueous solution of sodium bicarbonate (100 mL) and the resulting white precipitate collected by suction filtration, washed with water and dried in vacuo. The phenylmethyl [3-amino-1S-[[2R-hydroxy-3-[(3-methylbutyl)(methylsulfonyl)amino]-1S-(phenylmethyl) amino]carbonyl]-3-oxopropyl]carbamate was obtained as a white solid Anal. Calcd. for $C28H_{40}N_4O_7S$. 0.5 H_2O: C, 57.42; H, 7.06; N, 9.57. Found: C, 57.72; H, 7.21; N, 9.24.

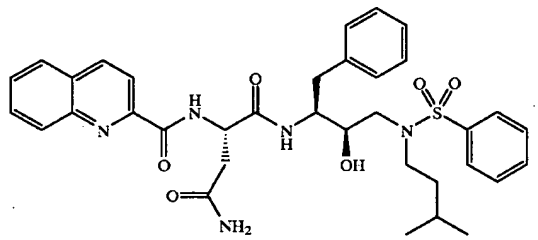
Part C

A solution of phenylmethyl [3-amino-1S-[[2R-hydroxy-3-[(3-methylbutyl)(methylsulfonyl)amino]-1S-(phenylmethyl)amino]carbonyl]-3-oxopropyl]carbamate (135 mg, 0.23 mmol) in methanol (15 mL) was hydrogenated over 10% palladium on carbon for 6 hours, filtered through diatomaceous earth and concentrated to give the product as an oil.

Part D

To a solution of the product from Part C (101 mg, 0.23 mmol) in DMF (5 mL) was added 2-quinoline carboxylic acid N-hydroxysuccinimide ester (67 mg, 0.25 mmol). The reaction was stirred at room temperature for 16 hours, then poured into a 50% saturated solution of sodium bicarbonate (60 mL). The resulting solid was collected by suction filtration washed with water and dried in vacuo. The N1-[2R-hydroxy-3-[(3-methylbutyl)(methylsulfonyl)-amino]-1S-(phenylmethyl)propyl]-2S-[(2-quinolinylcarbonyl)-amino]butanediamide was obtained as a white solid Anal. Calcd. for $C_{30}H_{39}N_5O_6S$. 0.1 H_2O: C, 58.52; H, 6.71; N, 11.37. Found: C, 58.34; H, 6.35; N, 11.13.

EXAMPLE 11B



Preparation of N1-[2R-hydroxy-3-[(3-methylbutyl)(phenylsulfonyl)amino]-1S-(phenylmethyl)propyl]-2S-[(2-quinolinylcarbonyl)amino]butanediamide

Part A

The CBZ protected compound phenylmethyl [2R-hydroxy-3-[(3-methylbutyl)(phenylsulfonyl)amino]-1S-(phenylmethyl)propyl]carbamate (200 mg, 0.38 mmol) was deprotected by hydrogenation over 10% palladium on carbon and the resulting product obtained as an oil.

Part B

The free amine from Part A was coupled with N-CBZ-L-asparagine (109 mg, 0.41 mmol) in the presence of N-hydroxybenzotriazole (63 mg, 0.41 mmol) and EDC (77 mg, 0.40 mmol) to give phenylmethyl[3-amino-1S-[[2R-hydroxy-3-[(3-methylbutyl)(phenylsulfonyl)amino]-1S-(phenylmethyl)amino]carbonyl]-3-oxopropyl]carbamate as a white solid. Anal. Calcd. for $C_{33}H_{42}N_4O_7S$: C, 62.05; H, 6.63; N, 8.77. Found: C, 61.86; H, 6.60; N, 8.64.

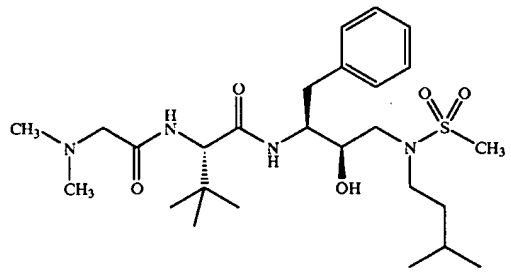
Part C

The product of Part B (110 mg, 0.17 mmol) was deprotected by hydrogenation over 10% palladium on carbon to give the product as an oil.

Part D

The resulting free amine was coupled with 2-quinoline carboxylic acid N-hydroxysuccinimide ester (45 mg, 0.17 mmol) to give N1-[2R-hydroxy-3-[(3-methylbutyl)(phenylsulfonyl)amino]-1S-(phenylmethyl)propyl]-2S-[(2-quinolinylcarbonyl)amino]butanediamide as a white solid. Anal. Calcd. for $C_{35}H_{41}N_5O_6S$: C, 63.71; H, 6.26; N, 10.61. Found: C, 63.59; H, 6.42; N, 10.42.

EXAMPLE 12A



Preparation of 2S-[[(dimethylamino)acetyl]amino]-N-[2R-hydroxy-3-[(3-methylbutyl)(methylsulfonyl)amino]-1S-(phenylmethyl)propyl]3,3-dimethylbutanamide

Part A

To a solution of N-CBZ-L-tert-leucine (100 mg, 0.38 mmol) and N-hydroxybenzotriazole (52 mg, 0.34 mmol) in DMF (3 mL) was added EDC (65 mg, 0.34 mmol). The solution was stirred for 60 minutes at room temperature and then the product of Example 10, Part A (105 mg, 0.32 mmol) in DMF (2 mL) was added. The reaction was stirred for 16 hours at room temperature, then poured into a 50% saturated solution of sodium bicarbonate (50 mL). The aqueous mixture was extracted twice with ethyl acetate (25 mL). The combined ethyl acetate layers were washed with water (25 mL) and dried over magnesium sulfate. Filtration and concentration produced an oil which was chromatographed on silica gel (50 gm) eluting with 2.5% methanol in dichloromethane. The phenylmethyl [1S-[[[2R-hydroxy-3-[(3-methylbutyl)(methylsulfonyl)amino]-1S-(phenylmethyl)propyl]amino]-carbonyl]-2,2-dimethylpropyl]carbamate was obtained as a gummy solid Anal. Calcd. for $C_{30}H_{45}N_3O_6S$ ◊ 2.2 H_2O: C, 58.55; H, 8.09; N, 6.83. Found: C, 58.38; H, 7.77; N, 7.10.

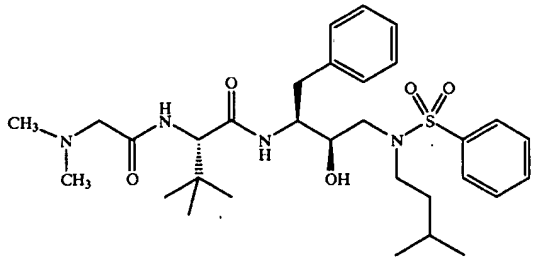
Part B

A solution of phenylmethyl[1S-[[[2R-hydroxy-3-[(3-methylbutyl)(methylsulfonyl)amino]-1S-(phenylmethyl)propyl]amino]carbonyl]-2,2-dimethylpropyl]carbamate (100 mg, 0.17 mmol) in methanol (10 mL) was hydrogenated over 10% palladium on carbon for 2 hours. The reaction was filtered through diatomaceous earth and concentrated to an oil.

Part C

N,N-dimethylglycine (20 mg, 0.19 mmol), N-hydroxybenzotriazole (28 mg, 0.18 mmol) and EDC (35 mg, 0.18 mmol) were stirred in DMF (4 mL) at room temperature for 40 minutes. The product from Part B in DMF (4 mL) was added and the reaction mixture stirred for 16 hours, then poured into a 50% saturated sodium bicarbonate solution (50 mL). The aqueous mixture was extracted three times with dichloromethane (30 mL) which in turn were washed with water (30 mL) and dried over magnesium sulfate. Filtration and concentration afforded an oil. The oil was chromatographed on silica gel (50 gm) eluting initially with 2.5% methanol in dichloromethane (400 mL) and then with 5% methanol in dichloromethane. The 2S-[[(dimethylamino)acetyl]amino]-N-[2R-hydroxy-3-[(3-methylbutyl)(methylsulfonyl)amino]-1S-(phenylmethyl)-propyl]-3,3-dimethylbutanamide was obtained as a white solid Anal. Calcd. for $C_{26}H_{46}N_4O_5S$ ◊ 0.5 CH_2Cl_2: C, 56.04; H, 8.34; N, 9.87. Found: C, 56.06; H, 8.36; N, 9.70.

EXAMPLE 12B



Preparation of 2S-[[(dimethylamino)acetyl]amino]-N-[2R-hydroxy-3-[(3-methyl-butyl)(phenylsulfonyl)amino]-1S-(phenylmethyl)propyl]-3,3-dimethylbutaneamide

Part A

To a solution of N-CBZ-L-tert-leucine (450 mg, 1.7 mmol) and N-hydroxybenzotriazole (260 mg, 1.7 mmol) in DMF (10 mL) was added EDC (307 mg, 1.6 mmol). The solution was stirred for 60 minutes at room temperature and then the product of Example 11, Part A (585 mg, 1.5 mmol) in DMF (2 mL) was added. The reaction was stirred for 16 hours at room temperature, then poured into a 50% saturated solution of sodium bicarbonate (200 mL). The aqueous mixture was extracted thrice with ethyl acetate (50 mL). The combined ethyl acetate layers were washed with water (50 mL) and saturated NaCl solution (50 mL), then dried over magnesium sulfate. Filtration and concentration produced an oil which was chromatographed on silica gel (50 gm) eluting with 20% ethyl acetate in hexane. The phenylmethyl[1S-[[[2R-hydroxy-3-[(3-methylbutyl)(phenylsulfonyl)amino]-1S-(phenylmethyl)propyl]amino]carbonyl]-2,2-dimethylpropyl]carbamate was obtained as a solid Anal. Calcd for $C_{35}H_{47}N_3O_6S$: C, 65.91; H, 7.43; N, 6.59. Found: C, 65.42; H, 7.24; N, 6.55.

Part B

A solution of phenylmethyl[1S-[[[2R-hydroxy-3-[(3-methylbutyl)(phenylsulfonyl)-amino]-1S-(phenylmethyl)propyl]amino]carbonyl]-2,2-dimethylpropyl]carbamate (200 mg, 0.31 mmol) in methanol (15 mL) was hydrogenated over 10% palladium on carbon for 2 hours. The reaction was filtered through diatomaceous earth and concentrated to an oil.

Part C

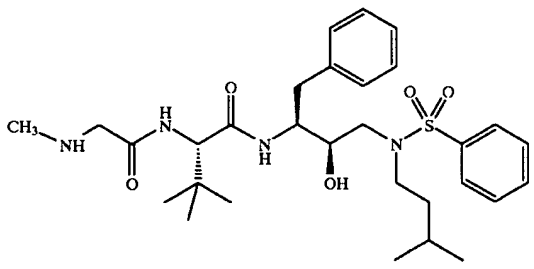
The resulting free amine from part B (150 mg, 0.3 mmol) was combined with diisopropylethylamine (114 uL, 0.33 mmol) in dichloromethane (5 mL). To this was added bromoacetyl chloride (27 uL, 0.33 mmol) dropwise. The reaction was stirred for 30 minutes at room temperature, then diluted with dichloromethane (30 mL) and extracted with 1 N HCl, water, and then saturated NaCl solution (25 mL each). The organic solution was dried over MgSO4 and concentrated to a solid. The 2S-[[bromoacetyl)amino]-N-[2R-hydroxy-3-[(3-methylbutyl)(phenylsulfonyl)amino]-1S-(phenylmethyl)propyl]-3,3-dimethylbutaneamide was sufficiently pure for use in the next step. This material can also be prepared by substituing bromoacetic anhydride for bromoacetyl chloride, or one can use chloroacetyl chloride or chloracetic anhydride.

Part D

The product from part C was dissolved in dichloromethane (5 mL) and diisopropylethylamine (114 uL, 0.66 mmol) and dimethylamine hydrochloride (53 mg, 0.66

mmol) were added. The reaction was stirred for 18 hours then concentrated under a stream of nitrogen to about 1 mL. The residue was chromatographed on silica gel (50 gm) using 2% methanol in dichloromethane. The 2S-[[(dimethylamino)-acetyl]amino]-N-[2R-hydroxy-3-[(3methylbutyl)-(phenylsulfonyl)amino]-1S-(phenylmethyl)propyl]-3,3-dimethylbutaneamide was obtained as a solid. Anal. Calcd for $C_{31}H_{48}N_4O_5S$: C, 63.24; H. 8.22; N, 9.52. Found: C, 63.03; H, 8.01; N, 9.40.

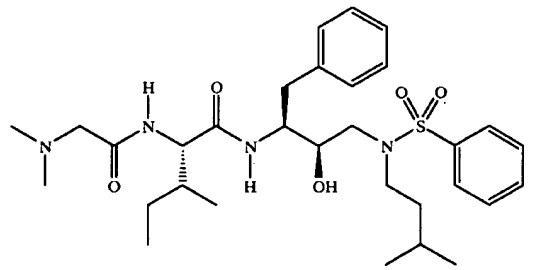
EXAMPLE 12C



Preparation of 2S-[[(methylamino)acetyl]amino]-N-[2R-hydroxy-3-[(3-methyl-butyl)(phenylsulfonyl)amino]-1S-(phenylmethyl)propyl]-3,3-dimethylbutaneamide

2S-[[bromoacetyl]amino]-N-[2R-hydroxy-3-[(3-methylbutyl)(phenylsulfonyl)amino]-1S-(phenylmethyl) propyl]-3,3-dimethylbutaneamide (103 mg, 0.16 mmol) and 40% aqueous methylamine (42 uL, 0.49 mmol) were combined in ethanol (2 mL) and stirred at room temperature for 24 hours. The reaction mixture was concentrated to dryness and triturated with ether. The solid material was removed by filtration and the filtrate concentrated to an oil. The oil was chromatographed on silica (50 gm) using 4% methanol in dichloromethane. The 2S-[[(methylamino)acetyl]amino]-N-[2R-hydroxy-3-[(3-methylbutyl)(phenylsulfonyl)amino]-1S-(phenylmethyl)propyl]-3,3-dimethylbutaneamide was obtained as a solid. Anal. Calcd for $C_{30}H_{46}N_4O_5S$: C, 62.69; H, 8.07; N, 9.75. Found: C, 62.38; H, 8.14; N, 9.60.

EXAMPLE 12D



Preparation of Pentanamide, 2S-[[(dimethylamino)) acetyl]amino]-N-[2R-hydroxy-3-[(3-methylbutyl) phenylsulfonyl)amino]-1S-(phenylmethyl)propyl] 3S-methyl

Part A

To a solution the amine product of Example 11, Part A; (2.79 g, 7.1 mmol) in 27 mL of dioxane was added (2.3 g, 7.1 mmol) of N-t-butylcarbonyl-L-isoleucine-N-hydroxysuccinamide ester, and the reaction was stirred under nitrogen atmosphere for 16 hours. The contents of the reaction were concentrated in vacuo, and the residue dissolved in ethyl acetate, washed with potassium hydrogen sulfate (5% aqueous), saturated sodium bicarbonate, and saturated sodium chloride. The organic layer was dried over magnesium sulfate, filtered and concentrated to yield 4.3 grams of crude material which was chromatographed using 3:1 ethyl acetate:hexane to obtain 3.05 g, 72% yield of Pentanamide, 2S-[[(1,1-dimethylethoxy)carbonyl]amino]-N-[2R-hydroxy-3-[(3-methylbutyl)phenylsulfonyl)amino]-1S-(phenylmethyl)propyl]-3-methyl.

Part B

(3.05 g, 5.0 mmol) of the product from Part A was dissolved in 20 mL of 4N HCl in dioxane and stirred under nitrogen atmosphere for 1.5 hours. The contents were concentrated in vacuo, and chased with diethyl ether. The crude hydrochloride salt was pumped on at 1 mm Hg until dry to yield 2.54 g of product as its hydrochloride salt.

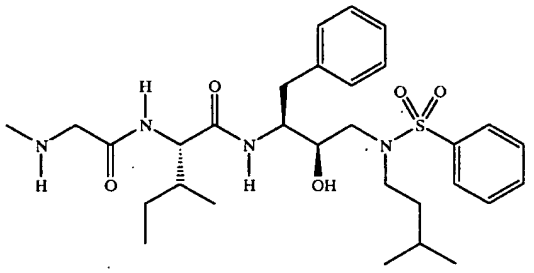
Part C

(2.54 g, 5.0 mmol) of amine hydrochloride was dissolved in 50 mL of tetrahydrofuran and to this was added (1.01 g, 10 mmol) of 4-methyl-morpholine, at which time a precipitate forms. To this suspension was added chloroacetic anhydride (0.865 g, 5.0 mmol) and stirred for 40 minutes. The contents were concentrated in vacuo, and the residue partitioned in ethyl acetate (200 mL) and 5% $KHSO_4$. The organic layer was washed with saturated sodium bicarbonate, and saturated sodium chloride, dried over magnesium sulfate, filtered and concentrated to yield the crude product. Purification by silica gel chromatography using an eluant of 1:1 ethyl acetate:hexanes yielded 1.89 grams of pure chloroacetamide.

Part D

To a solution of chloroacetamide (1.89 g, 3.2 mmol) from Part C, in 25 mL of tetrahydrofuran was added 4.0 mL of 50% aqueous dimethylamine and the solution was stirred for 1 hour. The solution was concentrated in vacuo and the residue was dissolved in ethyl acetate and washed with water. The organic layer was dried over magnesium sulfate, filtered and concentrated to yield the crude product which was purified by crystallization from ethyl acetate and isooctane to yield 1.80 g, (88% yield), mp.=121–122 C, HRes. MS. calc. 589.3424, found 589.3405.

EXAMPLE 12E

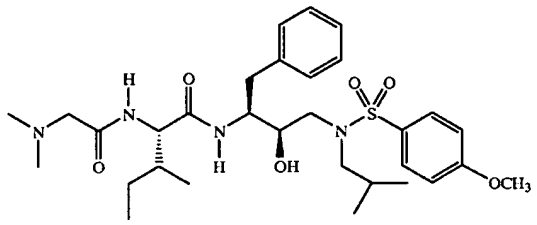


Preparation of Pentanamide, 2S-[[(Methylamino) acetyl]amino]-N-[2R-hydroxy-3-[(3-methylbutyl) (phenylsulfonyl)amino]-1S-(phenylmethyl)propyl]-3S-methyl

To a solution of the chloroacetamide of Example 12D, Part C, (2.36 g, 4.0 mmol) in tetrahydrofuran (25 mL) was added 3 mL of aqueous methylamine 40 wt %, and the

reaction stirred for 1 hour. The contents were concentrated and the residue was partitioned between ethyl acetate (100 mL) and water (100 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated to yield the crude product, which was purified by recrystallization from ethyl acetate heptane; (M+H)575, HRes.found 575.3267.

EXAMPLE 12F



Preparation of Pentanamide, 2S-[[(dimethylamino) acetyl]amino]-N-[2R-hydroxy-3-[(3-methylpropyl) (4-methoxyphenylsulfonyl)amino]-1S-(phenylmethyl) propyl]-3S-methyl

Part A

To a solution of 2R-hydroxy-3-[(2-methylpropyl) (4-methoxyphenylsulfonyl)amino]-1S-(phenylmethyl) propylamine (1.70 g, 4.18 mmol) in 40 mL of dichloromethane was added N-carbobenzyloxy-L-isoleucine-N-hydroxysuccinamide ester (1.51 g, 4.18 mmol) and the solution stirred under nitrogen atmosphere for 16 hours. The contents were concentrated in vacuo and the residue was redissolved in ethyl acetate. The ethyl acetate solution was washed with an aqueous solution of 5% $KHSO_4$, saturated sodium bicarbonate, and saturated sodium chloride, dried over magnesium sulfate, filtered, and concentrated to yield 2.47 g of crude product. The product was purified by silica gel chromatography using 1 2:1 hexane:ethyl acetate eluant to yield 2.3 g. (84% yield) of 2S-[(carbobenzyloxy)amino]-N-[2R-hydroxy-3-[(3-methylpropyl)(4-methoxyphenylsulfonyl)amino]-1S-(phenylmethyl)propyl]-3S-methylpentanamide.

Part B

(1.18 g, 1.8 mmol) of the product from Part A was dissolved in 50 mL of methanol, and to this was added 250 mg of 10% Palladium on carbon while under a stream of nitrogen. The suspension was hydrogenated using 50 psig of hydrogen for 20 hours. The contents were purged with nitrogen and filtered through celite, and concentrated in vacuo to yield 935 mg of 2S-(amino)-N-[2R-hydroxy-3-[(3-methylpropyl)(4-methoxyphenylsulfonyl)amino]-1S-(phenylmethyl)propyl]-3S-methylpentanamide, which was used without further purification.

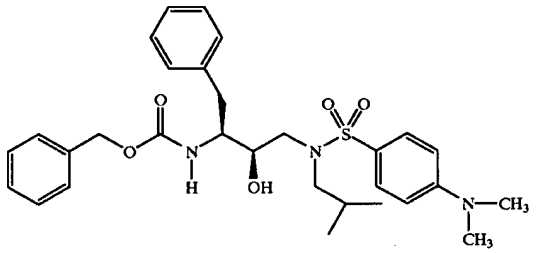
Part C

(0.935 g, 1.8 mmol) of the amine from Part B was dissolved in 15 mL of dioxane and to this was added (190 mg, 1.85 mmol) of 4-methylmorpholine folowed by (0.315 g, 1.8 mmol) of chloroacetic anhydride. The reaction mixture was stirred under nitrogen atmosphere for 3 hours, concentrated in vacuo, and redissolved in ethyl acetate. The ethyl acetate solution was washed with 50 mL of 5% agueous KHSO4, saturated $NaHCO_3$, and saturated NaCl solution, dried over $MgSO_4$, filtered and concentrated to yield 613 mg, (68% yield) of 2S-[(chloroacetyl)amino]-N-[2R-hydroxy-3-[(3-methylpropyl)(4-methoxyphenylsulfonyl)amino]-1S-(phenylmethyl)propyl]-3S-methylpentanamide, after purification by silica gel chromatography using 1:1 hexane:ethyl acetate.

Part D

To a solution of the chloroacetamide from Part C (673 mg, 1.10 mmol) in 20 mL of tetrahydrofuran was added 5 mL of 50 wt % aqueous dimethylamine and the solution was stirred for 1 hour. The reaction was concentrated and the residue was redissolved in 50 mL of ethyl acetate and washed with 25 mL of water. The ethyl acetate layer was dried over magnesium sulfate, filtered and concentrated to yield a crude solid which was purified by silica gel column chromatography using an eluant of 97:3 dichloromethane:methanol to proivde 400 mg of Pentanamide, 2S-[[dimethylamino) acetyl]amino]-N-[2R-hydroxy-3-[(3-methylpropyl)(4-methoxyphenylsulfonyl) amino]-1S-(phenylmethyl) propyl]-3S-methyl.

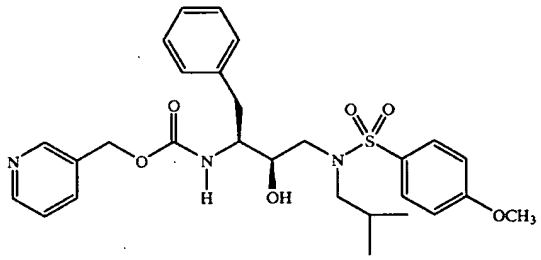
EXAMPLE 13A



Preparation of Carbamic acid, [2R-hydroxy-3-[[(4-dimethylaminophenyl)sulfonyl](2-methylpropyl) amino]-1S-(phenylmethyl)propyl]-, phenylmethyl ester

To a solution of 100 mg (0.19 mmol) of carbamic acid, [2R-hydroxy-3-[[(4-fluorophenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, phenylmethyl ester in 1 mL of pyridine was added 53 μL of triethylamine and 120 μL (p.95 mmol) of 40% aqueous dimethylamine. After heating for 24 hours at 100° C., the solution was cooled, ethyl acetate added, then washed with 5% citric acid, saturated sodium bicarbonate, dried over magnesium sulfate, filtered and concentrated. The resulting solid was recrystallized from ethyl acetate/hexane to afford 10 mg of the desired product; mass spectrum m/e=540 (M+H).

EXAMPLE 13B



Preparation of Carbamic acid, [2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 3-pyridylmethyl ester

Part A

A solution of N-benzyloxycarbonyl-3S-amino-1,2-S-epoxy-4-phenylbutane (50 g, 0.168 mol) and isobutylamine

(246 g, 3.24 mol) in 650 mL of isopropyl alcohol was refluxed for 1.25 hours. The solution was cooled to room temperature, concentrated in vacuo and then poured into 1 L of stirring hexane whereupon the product crystallized from solution, was collected and air dried to give 57.6 g of N-[3S-benzyloxycarbonylamino-2R-hydroxy-4-phenyl]-N-isobutylamine, mp 108–109.5° C., mass spectrum m/e=371 (M+H).

Part B

The amine from part A (1.11 g, 3.0 mmol) and triethylamine (324 mg, 3.20 mmol) in 20 mL of methylene chloride was treated with 715 mg (3.46 mmol) of 4-methoxybenzenesulfonyl chloride. The solution was stirred at room temperature for 6 hours, concentrated, dissolved in ethyl acetate, then washed with 1N potassium hydrogen sulfate, saturated sodium bicarbonate, brine, dried over magnesium sulfate, filtered and concentrated to afford a clear oil. This was recrystallized from diethyl ether to afford 1.27 g of carbamic acid, [2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, phenylmethyl ester, mp 97–101° C., mass spectrum m/e=541 (M+H).

Part C

A solution of 930 mg (3.20 mmol) of the product of part B in 30 mL of methanol was hydrogenated in the presence of 70 mg of a 10% palladium on carbon catalyst under 40 psig for 17 hours, the catalyst was removed by filtration, and the solution concentrated to afford 704 mg of [2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propylamine, mass spectrum m/e=407 (M+H), which was used directly in the next step without purification.

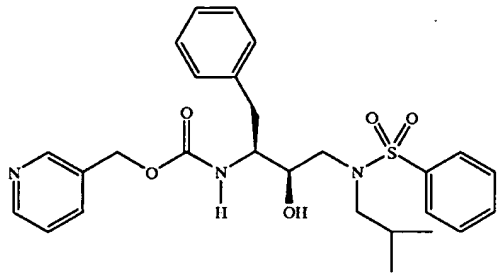
Part D

To a solution of 2.5 g (22.9 mmol) of 3-pyridylcarbinol in 100 mL of anhydrous acetonitrile was added 8.8 g (34.4 mmol) of N,N'-disuccinimidyl carbonate and 5.55 mL (68.7 mmol) of pyridine. The solution was stirred for 1 hour and then concentrated in vacuo. The residue was dissolved in ethyl acetate, then washed with saturated sodium bicarbonate, brine, dried over magnesium sulfate, filtered and concentrated to afford 5.3 g of N-Hydroxysuccinimide-3-pyridylmethyl carbonate, mass spectrum m/e=251 (M+H), which was used directly in the next step without purification.

Part E

To a solution of the amine from part C (2.87 g, 7.0 mmol) and 1.38 mL of triethylamine in 24 mL of anhydrous methylene chloride was added a solution of 1.65 g (6.6 mmol) of N-hydroxysuccinimide-3-pyridyl carbonate from part D in 24 mL of methylene chloride. The solution was stirred for 1 hour, 100 mL of methylene chloride added, then washed with saturated sodium bicarbonate, brine, dried over sodium sulfate, filtered and concentrated to afford 3.69 g of crude product. Chromatography on silica gel using 2% methanol/methylene chloride to afford 3.27 g of carbamic acid, [2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 3-pyridylmethyl ester, mass spectrum m/e=548 (M+Li).

EXAMPLE 13C



Preparation of Carbamic acid, [2R-hydroxy-3-[(phenylsulfonyl)(2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 3-pyridylmethyl ester

Part A

A solution of N-benzyloxycarbonyl-3S-amino-1,2-S-epoxy-4-phenylbutane (50 g, 0.168 mol) and isobutylamine (246 g, 3.24 mol) in 650 mL of isopropyl alcohol was refluxed for 1.25 hours. The solution was cooled to room temperature, concentrated in vacuo and then poured into 1 L of stirring hexane whereupon the product crystallized from solution, was collected and air dried to give 57.6 g of N-[3S-benzyloxycarbonylamino-2R-hydroxy-4-phenyl]-N-isobutylamine, mp 108–109.5 C, mass spectrum m/e=371 (M+H).

Part B

The amine from part A (0.94 g, 2.5 mmol) and triethylamine (288 mg, 2.85 mmol) in 20 mL of methylene chloride was treated with 461 mg (2.61 mmol) of benzenesulfonyl chloride. The solution was stirred at room temperature for 16 hours, concentrated, dissolved in ethyl acetate, then washed with 1N potassium hydrogen sulfate, saturated sodium bicarbonate, brine, dried over magnesium sulfate, filtered and concentrated to afford a clear oil. This was recrystallized from diethyl ether and hexane to afford 0.73 g of carbamic acid, [2R-hydroxy-3-[(phenylsulfonyl)(2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, phenylmethyl ester, mp 95–99 C, mass spectrum m/e=511 (M+H).

Part C

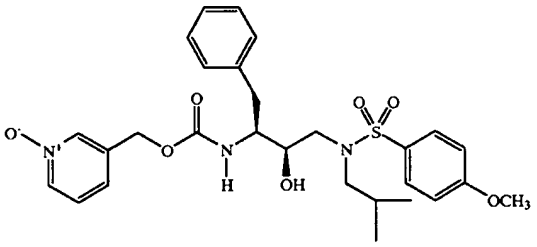
A solution of 500 mg of carbamic acid, [2R-hydroxy-3-[(phenylsulfonyl)(2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, phenylmethyl ester in 20 mL of methanol was hydrogenated in the presence of 250 mg of a 10% palladium on carbon catalyst under 40 psig for 3 hours, the catalyst was removed by filtration, and the solution concentrated to afford 352 mg of [2R-hydroxy-3-[(phenylsulfonyl])2-methylpropyl)amino]-1S-(phenylmethyl)propylamine, mass spectrum m/e=377 (M+H), which was used directly in the next step without purification.

Part D

To a solution of 1.24 mmol of 5-norbornene-2,3-dicarboximido carbonochloridate (Henklein, P., et. al., Synthesis 1987, 166–167) in 1 mL of anhydrous methylene chloride, was added a solution of 43 μL (2.44 mmol) of 3-pyridylcarbinol and 129 μL (1.6 mmol) of pyridine in 1 mL of methylene chloride at 0° C. under a nitrogen atmosphere. After 4 hours at room temperature, 150 mg (0.4 mmol) of [2R-hydroxy-3-[(phenylsulfonyl])2-methylpropyl)amino]-1S-(phenylmethyl)propylamine from Part C above was added and 100 μL of pyridine. After stirring for 15 hours at room temperature, ethyl acetate was added, then washed with 1N hydrochloric acid, saturated

sodium bicarbonate, brine, dried over magnesium sulfate, filtered and concentrated to afford 175 mg of crude product. Chromatography over silica gel using 1% methanol/methylene chloride to afford 69 mg of pure carbamic acid, [2R-hydroxy-3-[(phenylsulfonyl)(2-methylpropyl)amino]-1S-(phenylmethyl) propyl]-, 3-pyridylmethyl ester, mass spectrum m/e=512.2267 (M+H); calcd for $C_{27}H_{33}N_3O_5S$, 512.2219.

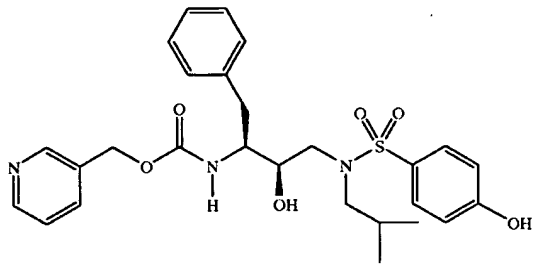
EXAMPLE 13D



Preparation of Carbamic acid, [2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 3-pyridylmethyl ester, N-oxide

To a solution of 211 mg (0.39 mmol) of carbamic acid, [2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 3-pyridylmethyl ester in 5 mL of methylene chloride at 0° C. was added 500 mg of 50% 3-chloroperbenzoic acid. After stirring at room temperature for 1 hour, ethyl acetate was added, the solution washed with saturated sodium bicarbonate, 0.2N ammonium hydroxide solution and brine, dried over magnesium sulfate, filtered and concentrated to afford 200 mg of crude product. This was chromatographed on C18 reverse phase material using 20–40% acetonitrile/water, then 100% acetonitrile to afford 90 mg of the desired product, which was then recrystallized from ethyl acetate/isooctane to yield 34 mg of pure carbamic acid, [2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl) amino]-1S-(phenylmethyl)propyl]-, 3-pyridylmethyl ester, N-oxide; mass spectrum m/e=564 (M+Li).

EXAMPLE 13E



Preparation of Carbamic acid, [2R-hydroxy-3-[[(4-hydroxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 3-pyridylmethyl ester

Part A

A solution of 0.98 g (1.85 mmol) of carbamic acid, [2R-hydroxy-3-[[(4-fluorophenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-phenylmethyl ester in 3.8 mL of anhydrous DMF was added to 22 mg (7.4 mmol) of 80% sodium hydride in 2 mL of DMF. To this mixture was added 0.40 g (3.7 mmol) of benzyl alcohol. After 2 hours, the solution was cooled to 0 C., water added, and then ethyl acetate. The organic layer was washed with 5% cirtic acid, saturated sodium bicarbonate and brine, dried over magnesium sulfate, filtered and concentrated to afford 0.90 g of crude material. This was chromatographed on basic alumina using 3% methanol/methylene chloride to afford 0.70 g of 2R-hydroxy-3-[(2-methylpropyl)(4-hydroxyphenyl)sulfonyl]amino-1S-(phenylmethyl)propylamine, cyclic carbamate; mass spectrum m/e=509(M+H).

Part B

To a solution of 0.65 g (1.28 mmol) of the cyclic carbamate from part A in 15 mL of ethanol, was added 2.6 mL (6.4 mmol) of 2.5N sodium hydroxide solution. After 1 hour at reflux, 4 mL of water was added and the solution refluxed for an additional eight hours. The volatiles were removed, ethyl acetate added, and washed with water, brine, dried over magnesium sulfate, filtered and concentrated to afford 550 mg of crude 2R-hydroxy-3-[(2-methylpropyl)(4-hydroxyphenyl) sulfonyl]amino-1S-(phenylmethyl) propylamine.

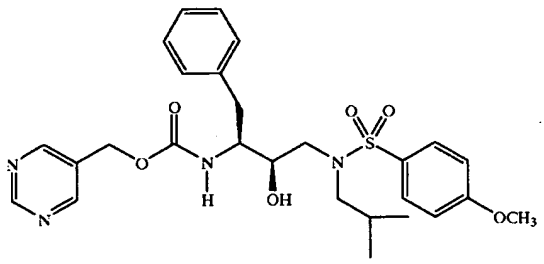
Part C

A solution of crude 2R-hydroxy-3-[(2-methylpropyl)(4-benzyloxyphenyl)sulfonyl]amino-1S-(phenylmethyl) propylamine in 10 mL of ethanol was hydrogenated in the presence of 500 mg of a 10% palldium on carbon catalyst under 50 psig of hydrogen for 2 hours. The catalyst was removed by filtration and the solvent removed in vacuo to afford 330 mg of 2R-hydroxy-3-[(2-methylpropyl)(4-hydroxyphenyl)sulfonyl]amino-1S-(phenylmethyl) propylamine, mass spectrum m/e=393 (M+H).

Part D

To a solution of 320 mg (0.82 mmol) of the amine from part C in 6 mL of DMF, was added 192 mg (0.76 mmol) of N-hydroxysuccinimide-3-pyridylmethyl carbonate. After 15 hours at room temperature, the DMF was removed in vacuo, ethyl acetate added, washed with water, brine, dried with magnesium sulfate, filtered and concentrated to afford 390 mg of crude material. Chromatogrpahy on silica gel using 50–80% ethyl acetate/hexane afforded 180 mg of carbamic acid, [2R-hydroxy-3-[[(4-hydroxyphenyl) sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 3-pyridylmethyl ester, mass spectrum m/e=528(M+H).

EXAMPLE 13F

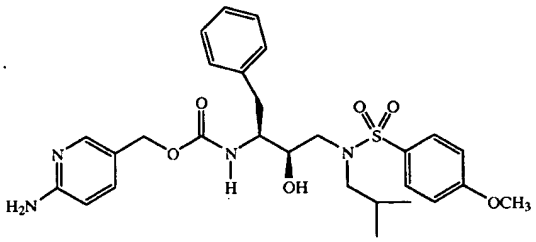


Preparation of Carbamic acid, [2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 5-pyrimidylmethyl ester

To a solution of 9.5 mg (0.09 mmol) of 5-pyrimidylcarbinol in 1 mL of anhydrous acetonitrile at

room temperature, was added 24 mg (0.09 mmol) of N,N'-disuccinimidyl carbonate and 19.1 μL (0.24 mmol) of pyridine. After stirring for 5 hours, 32 mg (0.08 mmol) of 2R-hydroxy-3-[(2-methylpropyl)(4-methoxyphenyl) sulfonyl]amino-1S-(phenylmethyl)propylamine was added and the solution stirred for 48 hours. After concentration in vacuo, methylene chloride was added, then washed with a 1:1 mixture of saturated sodium bicarbonate and brine, dried over magnesium sulfate, filtered and concentrated to give 27 mg of crude product. Chromatography on silica gel using 2% methanol/methylene chloride afforded 22 mg of the desired product, mass spectrum m/e=543(M+H).

EXAMPLE 13G



Preparation of Carbamic acid, [2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 3-(6-aminopyridyl) methyl ester

Part A: Prepartion of Ethyl 6-Aminonicotinate

To a suspension of 1.3 g (9.4 mmol) 6-aminonicotinic acid in 100 mL of ethanol, was bubbled in dry hydrochloric acid at 0° C., then the solution was refluxed until all the solids dissolved. The solvents were removed under reduced pressure, the residue dissolved in ethyl acetate, washed with saturated sodium bicarbonate, brine and concentrated to afford 1.37 g of a white solid, m/e=166(M+H).

Part B: Preparation of Ethyl 6-(tert-Butyloxycarbonylamino)nicotinate

A mixture of 848 mg (5.1 mmol) of ethyl 6-aminonicotinate from part A, 1.11 g (5.1 mmol) of di-tert-butylpyrocarbonate and 0.71 mL (5.1 mmol) of triethylamine in 10 mL of anhydrous toluene was refluxed for 15 hours. The solution was cooled, ethyl acetate added, washed with saturated sodium bicarbonate, brine, dried over anhydrous magnesium sulfate, filtered and concentrated to afford 1.28 g of the desired ethyl 6-(tert-butyloxycarbonylamino) nicotinate, m/e=267(M+H), which was used directly in the next step.

Part C: Preparation of 6-(tert-Butyloxycarbonylamino)-3-pyridylmethanol

To 4.6 mL (4.6 mmol) of a 1M solution of lithium aluminum hydride in diethyl ether at −40° C. under a nitrogen atmosphere, was added a slution of 618 mg (2.3 mmol) of ethyl 6-(tert-butyloxycarbonylamino)nicotinate from part B in 40 mL of anhydrous tetrahydrofuran. After the addition, this was warmed to room temperature, stirred for 3 hours, cooled to 0° C., and 145 μL of water, 145 μL of 20% sodium hydroxide solution and 290 μL of water were successively added. To the resulting mixture was added 50 mL of tetrahydrofuran and stirring continued for 30 minutes. Anhydrous magnesium sulfate was added, the solids removed via filtration and the filtrate concentrated under reduced pressure to afford 460 mg of the desired product, m/e=224(M+), which was used directly in the next step.

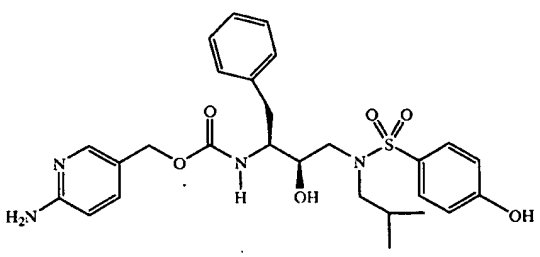
Part D: Preparation of Carbamic acid, [2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 3-[(6-tert-butyloxycarbonylamino)pyridyl]methyl ester

To a solution of 336 mg (1.5 mmol) of 6-(tert-butyloxycarbonylamino)-3-pyridylmethanol from part C in 14 mL of anhydrous acetonitrile at room temperature under a nitrogen atmosphere, was added 384 mg (1.5 mmol) of N,N'-disuccinimidyl carbonate and 364 μL (4.5 mmol) of anhydrous pyridine. After 4 hours, 406 mg (1 mmol) of 2R-hydroxy-3-[(2-methylpropyl)(4-methoxyphenyl) sulfonyl]amino-1S-(phenylmethyl)propylamine was added and stirring continued for 19 hours. The solvent was removed under reduced pressure, ethyl acetate added, washed with saturated sodium bicarbonate, brine, dried over magnesium sulfate, filtered and concentrated to afford 702 mg of crude product. Chromatography on silica gel using 1% methanol/methylene chloride as eluent afforded 170 mg of the desired carbamic acid, [2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 3-[(6-tert-butyloxycarbonylamino) pyridyl]methyl ester, m/e=663(M+Li).

Part E: Preparation of Carbamic acid, [2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl) amino]-1S-(phenylmethyl)propyl]-, 3-(6-aminopyridyl)methyl ester

To 5 mL of 4N hydrochloric acid in dioxane at room temperature, was added 150 mg (0.23 mmol) of carbamic acid, [2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 3-[(6-tert-butyloxycarbonylamino)pyridyl]methyl ester from part D. After stirring at room temperature for 28 hours, the solvent was removed under reduced pressure, the resulting solids triturated with diethyl ether, then dissolved in ethyl acetate and saturated sodium bicarbonate slution, separated, the organic layer washed with brine, dried with magnesium sulfate, filtered and concentrated. The residue was chromatographed on silica gel using 2.5% methanol/methylene chloride to yield 59 mg of the desired carbamic acid, [2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 3-(6-aminopyridyl)methyl ester, m/e=557(M+H).

EXAMPLE 13H



Preparation of Carbamic acid, [2R-hydroxy-3-[[(4-hydroxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 3-(6-aminopyridyl) methyl ester

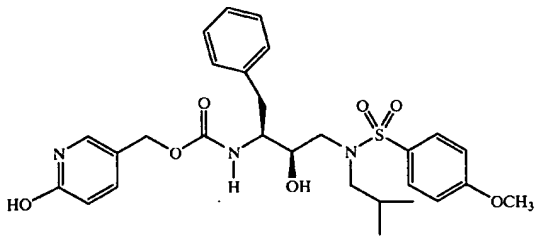
Part A: Preparation of Carbamic acid, [2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl) amino]-1S-(phenylmethyl)propyl]-, 3-[(6-tert-butyloxycarbonylamino)pyridyl]methyl ester

To a solution of 505 mg (2.25 mmol) of 6-(tert-butyloxycarbonylamino)-3-pyridylmethanol from in 20 mL of anhydrous acetonitrile at room temperature under a nitrogen atmosphere, was added 576 mg (2.25 mmol) of N,N'-disuccinimidyl carbonate and 546 μL (6.75 mmol) of anhydrous pyridine. After 1 hour, 837 mg (1.87 mmol) of 2R-hydroxy-3-[(2-methylpropyl)(4-hydroxyphenyl) sulfonyl]amino-1S-(phenylmethyl)propylamine was added and stirring continued for 3 hours. The solvent was removed under reduced pressure, ethyl acetate added, washed with saturated sodium bicarbonate, brine, dried over magnesium sulfate, filtered and concentrated to afford 1.37 g of crude product. chromatography on silica gel using 1% methanol/methylene chloride as eluent afforded 830 mg of material which was identified as a mixture of the desired carbamic acid, [2R-hydroxy-3-[[(4-hydroxyphenyl)sulfonyl](2-methylpropyl) amino]-1S-(phenylmethyl)propyl]-, 3-[(6-tert-butyloxycarbonylamino)pyridyl]methyl ester and the cyclic carbamate derived from the 2R-hydroxy-3-[(2-methylpropyl)(4-hydroxyphenyl)sulfonyl]amino-1S-(phenylmethyl)propylamine. The mixture was very difficult to separate, so was used as is in the next step.

Part B: Preparation of Carbamic acid, [2R-hydroxy-3-[[(4-hydroxyphenyl)sulfonyl](2-methylpropyl) amino]-1S-(phenylmethyl)propyl]-, 3-(6-aminopyridyl)methyl ester

To 830 mg of the mixture from part A, was added 50 mL of a 1:1 mixture of trifluoroacetic acid and methylene chloride. After 2.5 hours at room temperature, the solvent was removed under reduced pressure, ethyl acetate added, washed with saturated sodium bicarbonate, dried over magnesium sulfate, filtered and concentrated to afford 720 mg of crude material. This was chromatgraphed on silica gel using 5% methanol/ethyl acetate as eluent to yield 220 mg of product, which was recrystallized from methylene chloride/diethyl ether to afford 108 mg of the desired carbamic acid, [2R-hydroxy-3-[[(4-hydroxyphenyl)sulfonyl](2-methylpropyl) amino]-1S-(phenylmethyl)propyl]-, 3-(6-aminopyridyl)methyl ester, m/e=549(M+Li).

EXAMPLE 13I



Preparation of Carbamic acid, [2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 3-(6-hydroxypyridyl) methyl ester

Part A: Preparation of tert-Butyldimethylsilyl 6-(tert-butyldimethylsiloxy)nicotinate

To a solution of 5.0 g (35.9 mmol) of 6-hydroxynicotinic acid in 200 mL of anhydrous N,N-dimethylformamide at room temperature, was added 8.56 g (125 mmol) of imidazole and then 13.5 g (89 mmol) of tert-butyldimethylsilyl chloride. After 20 hours, the solvent was removed under reduced pressure, ethyl acetate added, washed with water, 5% citric acid, saturated sodium bicarbonate, brine, dried over anhydrous magnesium sulfate, filtered and concentrated to afford 10.5 g of crude material, m/e=368(M+H).

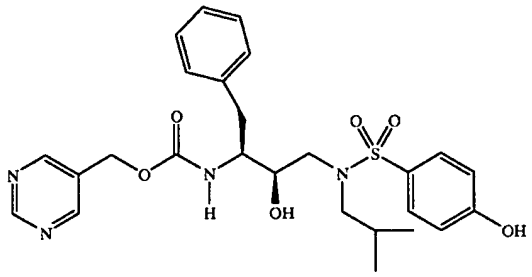
Part B: Preparation of 3-(6-tert-butyldimethylsiloxy) pyridylcarbinol

To 11 mL of 1M solution of lithium aluminum hydride in diethyl ether at −35° C. under a nitrogen atmosphere, was added a solution of 2.0 g (5.46 mmol) of product from part A in 20 mL of anhydrous diethyl ether. After 30 minutes, the reaction was warmed to 0° C. and stirred for 40 minutes. The solution was then quenched by the careful addition of 0.42 mL of water, 0.42 mL of 20% sodium hydroxide solution, and 0.84 mL of ater. Ethyl acetate was added, the precipate filtered and the organic phase concentrated to yield 0.93 g of crude 3-(6-tert-butyldimethylsiloxy)pyridylcarbinol, which was used directly in the next step.

Part C: Preparation of Carbamic acid, [2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl) amino]-1S-(phenylmethyl)propyl]-, 3-(6-hydroxypyridyl)methyl ester

To a solution of 860 mg (3.6 mmol) of material from part B in 15 mL of anhydrous acetonitrile, was added 919 mg (3.6 mmol) of N,N'-disuccinimidyl carbonate and 0.87 mL of pyridine. After 1 hour, 1.42 g(3.5 mmol) of 2R-hydroxy-3-[(2-methylpropyl)(4-methoxyphenyl)sulfonyl]amino-1S-(phenylmethyl)propylamine was added. After 14 hours at room temperature, the solvent was removed under reduced pressure, the residue disslved in ethyl acetate, washed with 5% citric acid, saturated sodium bicarbonate, brine, dried over magnesium sukfate, filtered and concentrated to afford 2.1 g of crude material. This was directly deprotected by dissolving in 40 mL of 80% acetic acid/water and stirring for 2 hours. The solvents were removed under reduced pressure, the residue dissolved in ethyl acetate, washed with saturated sodium bicarbonate, brine, dried over magnesium sulfate, filtered and concentrated to afford 1.7 g of crude product. This was chromatographed on silica gel using 50–100% ethyl acetate/hexane to provide a fraction of 0.19 g of fairly pure material, which was further purified by reverse phase chromatography using 15–40% acetonitrile/water (0.05% trifluoroacetic acid) to provide 120 mg of the desired carbamic acid, [2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 3-(6-hydroxypyridyl)methyl ester, m/e=558(M+H).

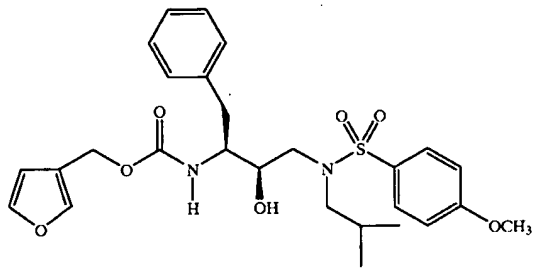
EXAMPLE 13J



Preparation of Carbamic acid, [2R-hydroxy-3-[[(4-hydroxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl], 5-pyrimidylmethyl ester

To a solution of 237 mg (2.15 mmol) of 5-pyrimidylcarbinol in 24 mL of anhydrous acetonitrile , was added 602 mg (2.35 mmol) of N,N'-disuccinimidyl carbonate and then 0.47 mL of pyridine. After stirring for 4.5 hours, 766 mg (1.96 mmol) of 2R-hydroxy-3-[(2-methylpropyl)(4-hydroxyphenyl)sulfonyl]amino-1S-(phenylmethyl)propylamine was added. After stirring for 19 hours, the solvent was removed under reduced pressure, ethyl acetate added, washed with 5% citric acid, saturated sodium bicarbonate, brine, dried over anhydrous magnesium sulfate, filtered and concentrated to afford 1.0 g of crude material. Chromatography on silica gel using 50–100% ethyl acetate/hexane as eluent afforded 450 mg of the desired carbamic acid, [2R-hydroxy-3-[[(4-hydroxyphenyl) sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl) propyl]-, 5-pyrimidylmethyl ester, m/e=529(M+H).

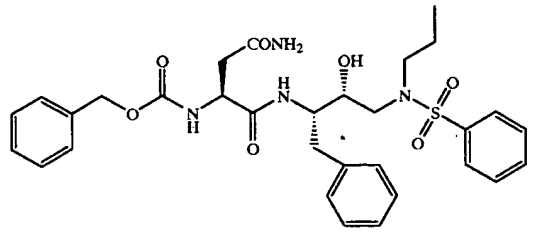
EXAMPLE 13K



Preparation of Carbamic acid, [2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, 3-furanylmethyl ester

To a solution of 98 mg (1 mmol) of 3-(hydroxymethyl) furan in 3 mL of anhydrous acetonitrile, was added 242 μL of pyridine and then 256 mg of N,N'-disuccinimidyl carbonate at room temperature under nitrogen. After 45 minutes, 406 mg (1 mmol) of 2R-hydroxy-3-[(2-methylpropyl)(4-methoxyphenyl)sulfonyl]amino-1S-(phenylmethyl)propylamine was added. After stirring at room temperature for 16 hours, ethyl acetate was added, washed with 5% citric acid, saturated sodium bicarbonate and brine, dried over magnesium sulfate, filtered and concentrated to afford 565 mg of crude product. This was chromatographed on silica gel using 50% ethyl acetate/hexane as eluent to afford 305 mg of a white foam, which was recrystallized from diethyl ether/hexane to yield 245 mg of pure carbamic acid, [2R-hydroxy-3-[[(4-methoxyphenyl) sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl) propyl-, 3-furanylmethyl ester, m/e=537(M+Li).

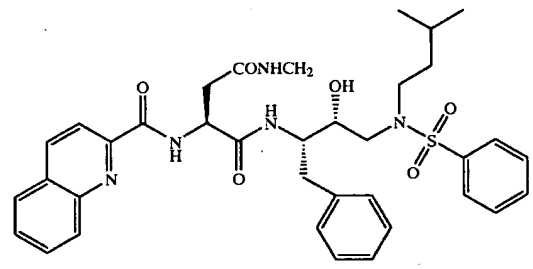
EXAMPLE 14



Preparation of phenylmethyl[3-amino-1S-[[2R-hydroxy-3-[(3-propyl)(phenylsulfonyl)amino]-1S-(phenylmethyl)amino]-carbonyl]-3-oxopropyl] carbamate

Phenylmethyl [2R-hydroxy-3-[(3-propyl) (phenylsulfonyl) amino]-1S-(phenylmethyl)propyl] carbamate (200 mg, 0.40 mmol) was deprotected by hydrogenation over 10% palladium on carbon and the resulting free amine was coupled with N-CBZ-L-asparagine (157 mg, 0.42 mmol) in the presence of N-hydroxybenzotriazole (114 mg, 0.84 mmol) and EDC (130 mg, 0.67 mmol) to give phenylmethyl[(3-amino-1S-[[2R-hydroxy-3-[(3-propyl) (phenylsulfonyl)amino]-1S-(phenylmethyl)amino] carbonyl]-3-oxopropyl]carbamate as a solid. Anal. Calcd for $C_{31}H_{38}N_4O_7S.0.2H_2O$: C,60.61; H,6.30; N,9.12. Found: C,60.27; H,6.16; N,8.93.

EXAMPLE 15A



Preparation of N^1-[2R-hydroxy-3-[(3-methylbutyl) (phenyl-sulfonyl)amino]-N^4-methyl-1S-(phenylmethyl)propyl]-2S-[(2-quinolinylcarbonyl) amino]butanediamide

Part A

N^2-[(1,1-dimethylethoxy)carbonyl]-N-methyl-L-asparagine was prepared from Boc-L-aspartic acid alpha-benzyl ester (1.0 g, 3.09 mmol), methylamine.HCl (209 mg, 3.09 mmol), EDC (711 mg, 3.7 mmol), 1-hydroxybenzotriazole (627 mg, 4.63 mmol), and N-methylmorpholine (0.7 mL, 6.3 mmol), in DMF (20 mL). After stirring overnight at room temperature, the reaction mixture was diluted with ethyl acetate, washed with water, saturated sodium bicarbonate, 5% citric acid, brine, dried over magnesium sulfate and concentrated to an oil. The oil

was taken up in 20 mL dry ethanol, and hydrogenated in the presence of 10% w/w of 10% Pd on C at atmospheric pressure and room temperature overnight. The mixture was filtered through Celite and concentrated to a white solid foam, 670 mg.

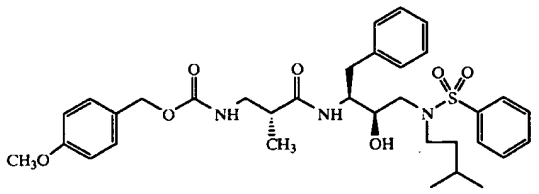
Part B

A solution of phenylmethyl [2R-hydroxy-3-[(3-methylbutyl) (phenylsulfonyl)amino]-1S-(phenylmethyl)-propyl]carbamate (310 mg, 0.59 mmol) in methanol (10 mL) was hydrogenated over 10% palladium on carbon for 3 h., filtered through diatomaceous earth and concentrated to give the product as an oil (214 mg). This free amine (208 mg, 0.53 mmol) was coupled with N2-[(1,1-dimethylethoxy)-carbonyl]-N-methyl-L-asparagine (137 mg, 0.56 mmol) in the presence of N-hydroxybenzotriazole (102 mg, 0.76 mmol) and EDC (130 mg, 0.67 mmol) to yield 290 mg of N1[2R-hydroxy-3-[(3-methylbutyl)(phenylsulfonyl)-amino]-N4-methyl-1S-(phenylmethyl)propyl]-2S-(1,1-dimethylethoxy-carbonyl)amino]butane diamide.

Part C

N^1[2R-hydroxy-3-[(3-methylbutyl)(phenyl-sulfonyl) amino]-N^4-methyl-1S-(phenylmethyl)propyl]-2S-[(1,1-dimethylethoxycarbonyl)-amino]butane diamide (270 mg, 0.43 mmol) was stirred in 4N HCl in dioxane (5 mL) at room temperature for 0.5 hr. Solvent and excess reagent were evaporated to dryness. The product was dried in vacuo. This material (125 mg, 0.225 mmol) was then reacted with 2-quinolinecarboxylic acid N-hydroxysuccimide ester (61 mg, 0.225 mmol), N-methylmorpholine (50 uL, 0.45 mmol) in methylene chloride (2 mL) for 3 h. The product N^1[2R-hydroxy-3-[(3-methylbutyl)(phenylsulfonyl)amino]-N^4-methyl-1S-(phenylmethyl)propyl]-2S-[(2-quinolinylcarbonyl)-amino]butanediamide was purified by silica gel chromatography. Anal. Calcd for $C_{36}H_{43}N_{506}S.0.2H_2O$: C,63.83; H,6.45; N,10.34. Found: C,63.64; H,6.40; N,10.34.

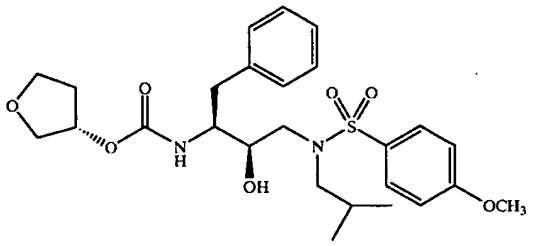
EXAMPLE 15B



Preparation of Carbamic acid, [3-[[2-hydroxy-3-[(3-methylbutyl)(phenylsufonyl)amino]-1-(phenylmethyl)propyl]amino]-2-methyl-3-oxopropyl]-, (4-methoxyphenyl)methyl ester, [1S-[1R*(S*),2S*]]

Carbamic acid, [2R-hydroxy-3-[(3-methylbutyl) (phenylsulphonyl)amino]-1S-(phenylmethyl)propyl]-, phenylmethyl ester (4.10 g, 7.8 mmol) was hydrogenated in a solution of methanol and ethanol using catalytic Pd/C 10% at 50 psig hydrogen for 3 hours. The catalyst was filtered and the solvents removed in vacuo to yield 3.0 grams of free amine. In a separate flask, 2.09 g, (7.8 mmol), of N-Moz-AMBA was added to 10 mL of dimethylformamide and 1.58 g, (1.5 equiv.), of N-hydroxybenzoltriazole and the solution was cooled to 5° C. To this solution was added 1.49 g, (7.8 mmol), of EDC and the solution stirred for 30 min. To this was added the free amine in 10 mL of dimethylformamide, and the reaction was stirred for 20 hours. The solvent was removed by evaporation and the crude material was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate. The ethyl acetate layer was washed with 5% potassium hydrogen sulfate and brine, dried over magnesium sulfate, filtered and concentrated to yield 2.58 grams (52%) of pure product after recrystallization from ethyl acetate, ether, and hexanes.

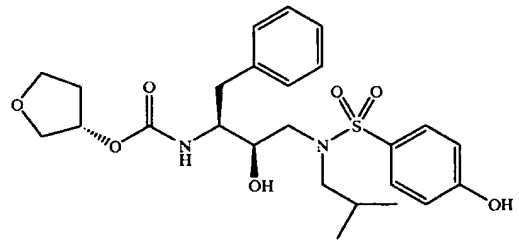
EXAMPLE 16A



Preparation of Carbamic acid, [2R-hydroxy-3-[(4-methoxyphenylsulfonyl) (2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, tetrahydrofuran-3S-yl ester

To a solution of 406 mg (1.0 mmol) of [2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propylamine in 5.0 mL of dichloromethane containing 150 mg (1.5 mmol) of triethylamine was added 280 mg (1.22 mmol) of N-succinimidyl-3S-tetrahydrofuranyl carbonate and the reacton mixture was stirred for 2 hours, an additonal 136 mg (0.3 mmol) of amine was added to the mixture and the solution stirred another 2 hours. The contents were diluted with 50 mL of ethyl acetate and washed with 5% aqueous citric acid, saturated sodium bicarbonate, and brine, then dried over magnesium sulfate, filtered and concentrated to yield 330 mg of crude product. Purification by silica gel chromatography using an eluant of 1:1 to 2:1 ethyl acetate/hexanes gradient provided Carbamic acid, [2R-hydroxy-3-[(4-methoxyphenylsulfonyl)(2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, tetrahydrofuran-3S-yl ester as a white solid. m/z=521 (M+H) calc. 521.2311 obs. 521.2311.

EXAMPLE 16B

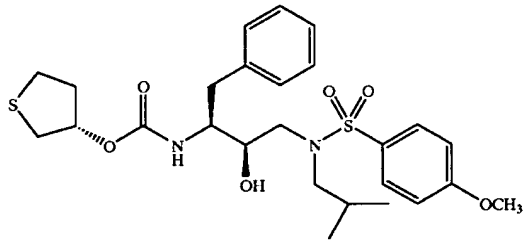


Preparation of Carbamic acid, [2R-hydroxy-3-[(4-hydroxyphenylsulfonyl) (2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, tetrahydrofuran-3S-yl ester

To a solution of 435 mg (1.0 mmol) of [2R-hydroxy-3-[[(4-hydroxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-

(phenylmethyl)propylamine in 3.0 mL of dimethylformamide was added 225 mg (0.98 mmol) of N-succinimidyl-3S-tetrahydrofuranylcarbonate and the solution was stirred overnight. The mixture was diluted with 50 mL of ethyl acetate and washed with 5% aqueous citric acid, saturated sodium bicarbonate, and brine, dried over magnesium sulfate, filtered and concentrated to yield 515 mg of crude product. Purificaton by silica gel chromatography using and eluant of 1:1 ethyl acetate: hexanes provided 315 mg of Carbamic acid, [2R-hydroxy-3-[(4-hydroxyphenylsulfonyl)(2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, tetrahydrofuran-3S-yl ester, as a white solid. HRMS calc. 507.2165, obs. 507.2155.

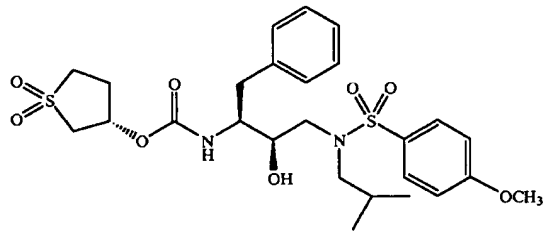
EXAMPLE 16C



Preparation of Carbamic acid, [2R-hydroxy-3-[(4-methoxyyphenylsulfonyl)(2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, tetrahydrothiophen-3S-yl ester

To a solution of 215 mg (2.0 mmol) of 3S-hydroxythiophene, 415 μL of anhydrous pyridine, and 2 mL of dry acetonitrile was added 512 mg (2.0 mmol) of N,N'-Dimethylsuccinimidyl carbonate and this suspension was stirred for 45 minutes. To this clear solution was added a solution of 700 mg (1.7 mmol) of [2R-hydroxy-3-[[(4-methoxyyphenyl) sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl) propylamine in 2.0 mL of acetonitrile and stirred for 12 hours. The contents were concentrated, and the residue was partitioned between ethyl acetate and 5% aqueous potassium hydrogen sulfate. The organic layer was washed with saturated sodium bicarbonate and then brine, dried over sodium sulfate, filtered and concentrated to yield 780 mg of crude material. Purificaton by silica gel chromatograpy using an eluant of 10:10:1 ethyl acetate: hexane:methanol provided 520 mg of Carbamic acid, [2R-hydroxy-3-[(4-methoxyphenylsulfonyl)(2-methylpropyl) amino]-1S-(phenylmethyl)propyl-, tetrahydrothiophen-3S-yl-ester, as a crystalline white solid. m.p.=162–3° C., m/z=553 (M+H).

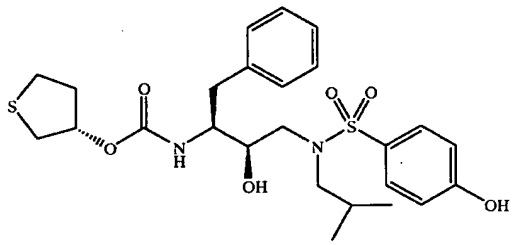
EXAMPLE 16D



Preparation of Carbamic acid, [2R-hydroxy-3-[(4-methoxyphenylsulfonyl)(2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, 1,1-dioxotetrahydrothiophen-3S-yl ester

To a solution of 270 mg (0.5 mmol) of Carbamic acid, [2R-hydroxy-3-[(4-methoxyphenylsulfonyl)(2-methylpropyl) amino]-1S-(phenylmethyl)propyl-, tetrahydrothiophen-3S-yl ester in 30 mL of dichloromethane was added 400 mg (1.2 mmol) of m-chloroperbenzoic acid (50 wt %) and the mixture was stirred for 12 hours. The contents were diluted with 10 mL of 10% aqueous sodium metabisulfite and stirred for 30 minutes. The organic layer was washed with saturated sodium bicarbonate, dried over sodium sulfate, filtered and concentrated to yield 290 mg of crude product. Purification by silica gel chromatography using an eluant of 10:10:1 ethyl acetate:hexane:methanol provided 260 mg of Carbamic acid, [2R-hydroxy-3-[(4-methoxyphenyl sulfonyl)(2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, 1,1-dioxotetrahydrothiophen-3S-yl ester, as a white crystalline solid. m.p.=69° C., m/z=569 (M+H).

EXAMPLE 16E

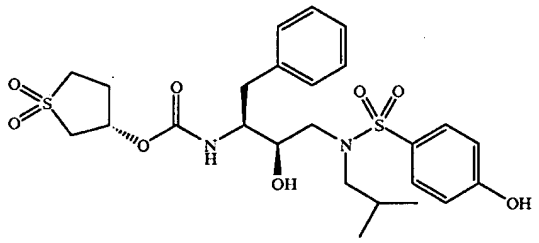


Preparation of Carbamic acid, [2R-hydroxy-3-[(4-hydroxyphenylsulfonyl)(2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, tetrahydrothiophen-3S-yl ester

To a solution of 125 mg (1.2 mmol) of 3-S-hydroxythiophene, 250 μL of anhydrous pyridine,and 1 mL of dry acetonitrile was added 307 mg (1.2 mmol) of N,N'-dimethylsuccinimidyl carbonate and this suspension was stirred for 45 minutes. To this clear solution was added a solution of 445 mg (1.0 mmol) [2R-hydroxy-3-[[(4-hydroxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propylamine in 1.0 mL of acetonitrile and stirred for 12 hours. The contents were concentrated, and the

residue was partitioned between ethyl acetate and 5% aqueous potassium hydrogen sulfate. The organic layer was washed with saturated sodium bicarbonate and then brine, dried over sodium sulfate, filtered and concentrated to yield 460 mg of crude material. Purificaton by silica gel chromatograpy using an eluant of 10:10:1 ethyl acetate: hexane:methanol provided 235 mg of Carbamic acid, [2R-hydroxy-3-[(4-hydroxyphenyl sulfonyl)(2-methylpropyl) amino]-1S-(phenylmethyl)propyl-, tetrahydrothiophen-3S-yl ester, as a crystalline white solid. m.p.=184–85° C., m/z=529 (M+Li).

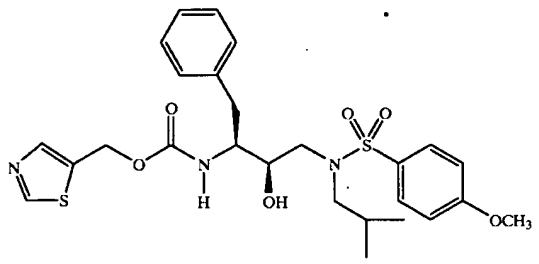
EXAMPLE 16F



Preparation of Carbamic acid, [2R-hydroxy-3-[(4-hydroxyphenylsulfonyl)(2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, 1,1-dioxotetrahydrothiophen-3S-yl ester

To a solution of 125 mg (0.24 mmol) of carbamic acid, [2R-hydroxy-3-[(4-hydroxyphenylsulfonyl)(2-methylpropyl) amino]-1S-(phenylmethyl)propyl-, tetrahydrothiophen-3S-yl ester in 30 mL of dichloromethane was added 240 mg (0.7 mmol) of m-chloroperbenzoic acid (50 wt %) and the mixture was stirred for 12 hours. The contents were diluted with 5 mL of 10% aqueous sodium metabisulfite and stirred for 30 minutes. The organic layer was washed with saturated sodium bicarbonate, dried over sodium sulfate, filtered and concentrated to yield 110 mg of crude product. Purification by silica gel chromatography using an eluant of 1:1 to 2:1 ethyl acetate:hexane:methanol provided 100 mg of carbamic acid, [2R-hydroxy-3-[(4-hydroxyphenyl sulfonyl)(2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, 1,1-dioxotetrahydrothiophen-3S-yl-ester, as a white crystalline solid, m.p.=190° C., m/z=561 (M+Li).

EXAMPLE 17A



Preparation of Carbamic acid, [2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 5-thiazolylmethyl ester

Part A: Preparation of Methyl 2-aminothiazole-5-carboxylate

Methyl chloroacetate 190 g (1.75 mol) and methyl formate 111 g (1.80 mol), were added dropwise to a suspension of 100 g (1.8 mol.) of sodium methoxide in 450 mL of dry toluene at 5° C. over 2 hours. After an additional 2.5 hours at 0° C. The contents were diluted with 600 mL of water and the layers separated. The aqueous phase was acidified with 113 mL of concentrated hydrochloric acid. The aqueous solution was placed in a 2 liter flask and 175 grams of thiourea was added and to solution was heated to reflux for 1.45 hours. To the cooled solution was added 25 g of DARCO activated charcoal and filtered through filter paper. The crude dark yellow solution was neutralized with 2.5 N sodium hydroxide upon which time an amber solid precipitated which was filtered and air dried to yield 147 g of desired methyl 2-aminothiazole-5-carboxylate. m/e=159 (M+H).

Part B: Preparation of Methyl 5-thiazolecarboxylate

To a solution of 35 mL (30.5 g, 260 mmol) of isoamyl nitrite in 120 mL of dioxane at 80° C. under nitrogen, was slowly added a slurry of 20.0 g (126 mmol) of methyl 2-amino-5-thiazolecarboxylate over a 45 minute period. After refluxing for a further 1 hour, the solution was cooled, concentrated, dissolved in ethyl acetate, washed with saturated sodium bicarbonate, brine, dried over magnesium sulfate, filtered and concentrated to afford 28 g of the crude product. This was chromatographed on 400 g of silica gel using 20% ethyl acetate/hexane to afford 9.07 g of purified material, which was crystallized from methylene chloride/hexane to yield 7.64 g of pure methyl 5-thiazolylcarboxylate, m/e=144(M+H).

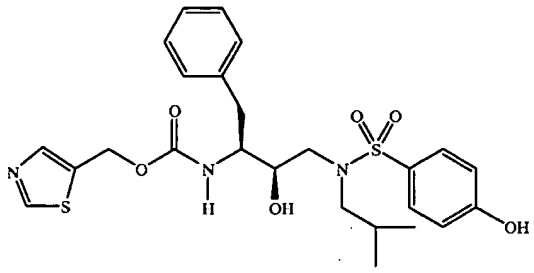
Part C: Preparation of 5-thiazolemethanol

To a solution of 11.73 g (82 mmol) of methyl 5-thiazolylcarboxylate in 105 mL of anhydrous tetrahydrofuran at 0° C. under nitrogen, was added 90 mL (90 mmol) of a 1.0M lithium aluminum hydride solution in diethyl ether over a 35 minute period. After stiiring at room temperature for 30 minutes, the solution was cooled to 0° C., and carefully quenched by the addition of 3 mL of water, 3 mL of 20% sodium hydroxide solution, and 6 mL of water, then 100 mL of tetrahydrofuran was added. After stirring for 1 hour, the mixture was filtered, the solid was washed with tetrahydrofuran, and the filtrate concentrated to afford 7.56 g of 5-thiazolylmethanol.

Part D: Preparation of Carbamic acid, [2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 5-(thiazolyl)methyl ester

To a solution of 115 mg (1.00 mmol) of 5-(hydroxymethyl) thiazole in 3 mL of anhydrous acetonitrile, was added 0.25 mL (0.25 g, 3.09 mmol) of pyridine and then 256 mg (1.03 mmol) of N,N'-disuccinimidyl carbonate at room temperature under nitrogen. After 45 minutes, 406 mg (1.00 mmol) of 2R-hydroxy-3-[(2-methylpropyl)(4-methoxyphenyl)sulfonyl]amino-1S-(phenylmethyl)propylamine was added. After stirring at room temperature for 15 hours, ethyl acetate was added, washed with water, saturated sodium bicarbonate and brine, dried over magnesium sulfate, filtered and concentrated to afford 500 mg of crude product. This was chromatographed on silica gel using 80% ethyl acetate/hexane as eluent to afford 307 mg of a white solid, which was identified as the desired carbamic acid, [2R-hydroxy-3-[[(4-methoxyphenyl) sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl) propyl-, 5-thiazolylmethyl ester, m/e=548(M+H).

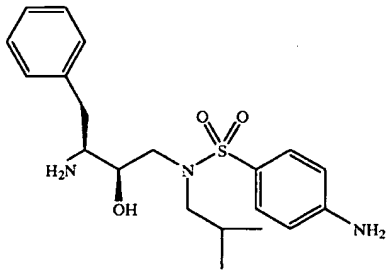
EXAMPLE 17B



Preparation of Carbamic acid, [2R-hydroxy-3-[[(4-hydroxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, 5-thiazolylmethyl ester

To a solution of 115 mg (1.00 mmol) of 5-(hydroxymethyl) thiazole in 3 mL of anhydrous acetonitrile, was added 0.25 mL (0.25 g, 3.09 mmol) of pyridine and then 256 mg (1.03 mmol) of N,N'-disuccinimidyl carbonate at room temperature under nitrogen. After 45 minutes, 392 mg (1.00 mmol) of 2R-hydroxy-3-[(2-methylpropyl)(4-hydroxyphenyl) sulfonyl]amino-1S-(phenylmethyl)propylamine was added. After stirring at room temperature for 15 hours, ethyl acetate was added, washed with water, saturated sodium bicarbonate and brine, dried over magnesium sulfate, filtered and concentrated to afford 450 mg of crude product. This was chromatographed on silica gel using 80% ethyl acetate/hexane as eluent to afford 270 mg of a white solid, which was identified as the desired carbamic acid, [2R-hydroxy-3-[[(4-hydroxyphenyl) sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl) propyl-, 5-thiazolylmethyl ester, m/e=534 (M+H).

EXAMPLE 18A



Preparation of 2R-hydroxy-3-[[(4-aminophenyl) sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl) propylamine

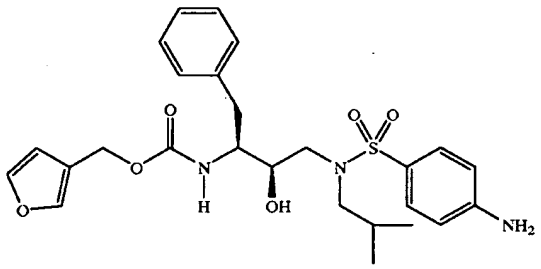
Part A: Preparation of Carbamic acid, 2R-hydroxy-3-[[(4-nitrophenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, phenylmethyl ester

To a solution of 4.0 g (10.8 mmol) of N-[3S-benzyloxy carbonylamino-2R-hydroxy-4-phenyl]-N-isobutylamine in 50 mL of anhydrous methylene chloride, was added 4.5 mL (3.27 g, 32.4 mmol) of triethylamine. The solution was cooled to 0° C. and 2.63 g (11.9 mmol) of 4-nitrobenzene sulfonyl chloride was added, stirred for 30 minutes at 0° C., then for 1 hour at room temperature. Ethyl acetate was added, washed with 5% citric acid, saturated sodium bicarbonate, brine, dried and concentrated to yield 5.9 g of crude material. This was recrystallized from ethyl acetate/hexane to afford 4.7 g of pure carbamic acid, [2R-hydroxy-3-[[(4-nitrophenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, phenylmethyl ester, m/e=556(M+H).

Part B: Preparation of 2R-hydroxy-3-[[(4-aminophenyl) sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl) propylamine

A solution of 3.0 g (5.4 mmol) of carbamic acid, 2R-hydroxy-3-[[(4-nitrophenyl)sulfonyl](2-methylpropyl) amino]-1S-(phenylmethyl)propyl-, phenylmethyl ester in 20 mL of ethyl acetate was hydrogenated over 1.5 g of 10% palladium-on-carbon catalyst under 35 psig of hydrogen for 3.5 hours. The catalyst was removed by filtration and the solution concentrated to afford 2.05 g of the desired 2R-hydroxy-3-[[(4-aminophenyl)sulfonyl](2-methylpropyl) amino]-1S-(phenylmethyl) propylamine, m/e=392 (M+H).

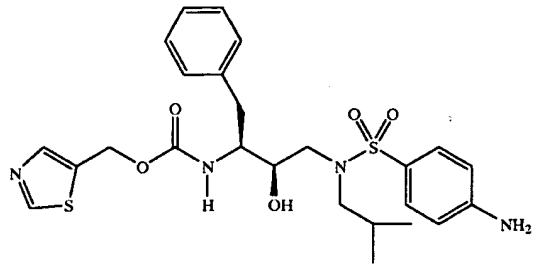
EXAMPLE 18B



Preparation of Carbamic acid, 2R-hydroxy-3-[[(4-aminophenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, 3-furanylmethyl ester

To a solution of 104 mg (1.06 mmol) of 3-(hydroxymethyl) furan in 2 mL of anhydrous acetonitrile, was added 0.26 mL (0.25 g, 3.18 mmol) of pyridine and then 277 mg (1.06 mmol) of N,N'-disuccinimidyl carbonate at room temperature under nitrogen. After 45 minutes, 415 mg (1.06 mmol) of 2R-hydroxy-3-[(2-methylpropyl)(4-aminophenyl)sulfonyl]amino-1S-(phenylmethyl) propylamine was added. After stirring at-room temperature for 72 hours, ethyl acetate was added, washed with 5% citric acid, saturated sodium bicarbonate and brine, dried over magnesium sulfate, filtered and concentrated to afford 550 mg of crude product. This was chromatographed on silica gel using 50% ethyl acetate/hexane as eluent to afford 230 mg of a white foam, which was identified as the desired carbamic acid, 2R-hydroxy-3-[[(4-aminophenyl)sulfonyl] (2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, 3-furanylmethyl ester, m/e=522 (M+Li).

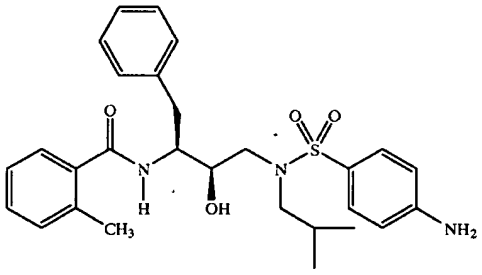
EXAMPLE 18C



Preparation of Carbamic acid, 2R-hydroxy-3-[[(4-aminophenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, 5-thiazolylmethyl ester

To a solution of 118 mg (1.03 mmol) of 5-(hydroxymethyl) thiazole in 3 mL of anhydrous acetonitrile, was added 0.25 mL (0.24 g, 3.09 mmol) of pyridine and then 264 mg (1.03 mmol) of N,N'-disuccinimidyl carbonate at room temperature under nitrogen. After 45 minutes, 403 mg (1.03 mmol) of 2R-hydroxy-3-[(2-methylpropyl)(4-aminophenyl)sulfonyl]amino-1S-(phenylmethyl)propylamine was added. After stirring at room temperature for 15 hours, ethyl acetate was added, washed with 5% citric acid, saturated sodium bicarbonate and brine, dried over magnesium sulfate, filtered and concentrated to afford 350 mg of crude product. This was chromatographed on silica gel using 80% ethyl acetate/hexane as eluent to afford 290 mg of a white solid, which was identified as the desired carbamic acid, 2R-hydroxy-3-[[(4-aminophenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, 5-thiazolylmethyl ester, m/e=539 (M+Li).

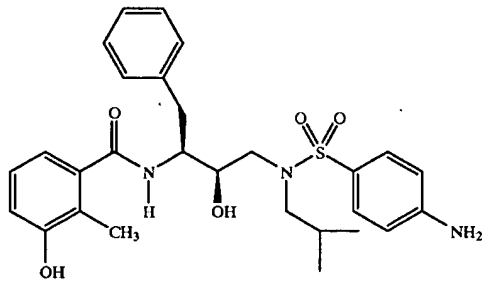
EXAMPLE 18D



Preparation of Benzamide, N-[2R-hydroxy-3-[[(4-aminophenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-2-methyl

To a solution of 391 mg (1 mmol) of 2R-hydroxy-3-[(2-methylpropyl)(4-aminophenyl)sulfonyl]amino-1S-(phenylmethyl)propylamine in 3 mL of anhydrous methylene chloride, was added 0.42 mL (3 mmol) of triethylamine, then at room temperature, 0.12 mL (0.9 mmol) of orthotoluoyl chloride was added. After 15 hours at room temp ethyl acetate was added, washed with 5% citric acid, saturated sodium bicarbonate, brine, dried, filtered and concentrated to afford 420 mg of crude material. This was chromatographed on 40 g of silica gel using 50% ethyl acetate/hexane to afford 368 mg of pure benzamide, N-[2R-hydroxy-3-[[(4-aminophenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-2-methyl, m/e=516(M+Li).

EXAMPLE 18E



Preparation of Benzamide, N-[2R-hydroxy-3-[[(4-aminophenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-3-hydroxy-2-methyl

Part A: Preparation of 3-Hydroxy-2-methylbenzoic Acid

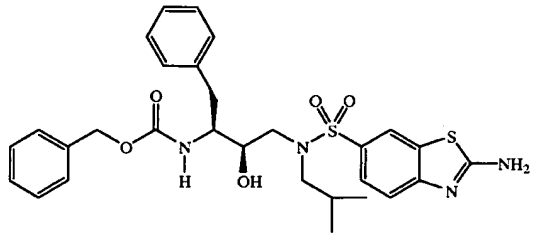
A one-necked 100 mL round-bottomed flask (magnetic stirring) was charged with 1.0 gram (6.6 mM) 3-amino-2-methylbenzoic acid. A warm mixture of 2.3 mL conc. sulfuric acid in 4.3 mL water was added to the flask, the resulting slurry was cooled below 15° C. in an ice bath, and 6.6 grams of ice was added. The reaction mixture was treated via subsurface addition with a solution of 0.6 gram (8.6 mM) sodium nitrite in 6.6 mL ice water with the reaction temperature maintained at 0–5° C. during the addition. After stirring at 0–5° C. for 30 min., a few crystals of urea were added to decompose the excess nitrite. The reaction mixture was then poured into a room temperature solution of 23.8 grams (102.3 mM) copper (II) nitrate hemipentahydrate in 200 ML water. With vigorous stirring, the reaction mixture was treated with 0.9 gram (6.0 mM) copper (I) oxide. The reaction mixture foamed and changed from turquoise blue to dark green in color. Reaction was left stirring for 30 min. The reaction mixture was extracted with diethyl ether (3X), and the organic extracts were combined. The organic extracts were concentrated to approximately one-fourth the original volume, then extracted with 25 mL 1N sodium hydroxide solution. The layers were separated, and the dark-red aqueous layer was acidified to pH=2 using 1N hydrochloric acid solution. The acidified aqueous layer was then extracted with diethyl ether (3X), and the ether extracts were combined, dried (MgSO4), and concentrated to yield a reddish-colored oil. Purification by flash chromatography on silica gel using a gradient of 0–7% methanol/methylene chloride afforded 0.39 grams (36%) of a yellow solid.

Part B: Preparation of Benzamide, N-[2R-hydroxy-3-[[(4-aminophenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-3-hydroxy-2-methyl

To a solution of 175 mg (1.15 mmol) of 3-hydroxy-2-methylbenzoic acid and 203 mg (1.5 mmol) of N-hydroxybenzotriazole in 6 mL of anhydrous N,N-dimethylformamide at 0° C., was added 220 mg (1.15 mmol) of EDC. After 20 minutes of activation at 0° C. and 1 hour

at room temperature, 392 mg (1.0 mmol) of 2R-hydroxy-3-[(2-methylpropyl)(4-aminophenyl)sulfonyl]amino-1S-(phenylmethyl)propylamine was added. After 15 hours at room temperature, ethyl acetate was added, washed with 5% citric acid, saturated sodium bicarbonate, brine, dried, filtered and concentrated to afford 590 mg of crude material. This was chromatographed on silica gel using 50–80% ethyl acetate/methylene chloride as eluent to afford 255 mg of pure benzamide, N-[2R-hydroxy-3-[[(4-aminophenyl) sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl) propyl]-3-hydroxy-2-methyl, m/e=526(M+H).

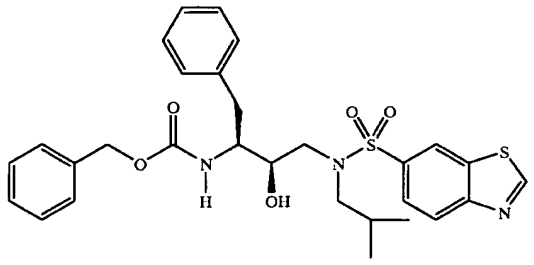
EXAMPLE 18F



Preparation of Carbamic acid, 2R-hydroxy-3-[[(2-aminobenzothiazol-6-yl) sulfonyl](2-methylpropyl) amino]-1S-(phenylmethyl)propyl-, phenylmethyl ester

Carbamic acid, 2R-hydroxy-3-[[(4-aminophenyl) sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl) propyl-, phenylmethyl ester 0.30 g (0.571 mmol) was added to a well mixed powder of anhydrous copper sulfate (1.20 g) and potassium thiocyanate (1.50 g) followed by dry methanol (6 mL) and the resulting black-brown suspension was heated at reflux for 2 hrs. The reaction mixture was filtered and the filtrate was diluted with water (5 mL) and heated at reflux. Ethanol was added to the reaction mixture, cooled and filtered. The filtrate upon concentration afforded a residue which was chromatographed (ethyl acetate:hexane 80:20) to afford 0.26 g (78%) of the desired compound as a solid.

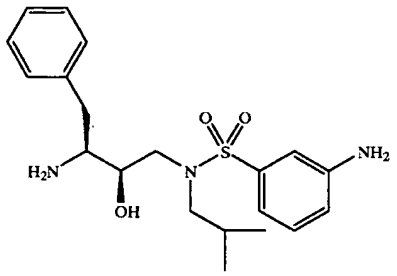
EXAMPLE 18G



Preparation of Carbamic acid, 2R-hydroxy-3-[[(benzothiazol-6-yl)sulfonyl](2-methylpropyl) amino]-1S-(phenylmethyl)propyl-, phenylmethyl ester

Carbamic acid, 2R-hydroxy-3-[[(2-aminobenzothiazol-6-yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl) propyl-, phenylmethyl ester (0.25 g, 0.429 mmol) was added to a solution of isoamylnitrite (0.116 mL, 0.858 mmol) in dioxane (5 mL) and the mixture was heated at 85° C. After the cessation of evolution of nitrogen, the reaction mixture was concentrated and the residue was purified by chromatography (hexane:ethyl acetate 5:3) to afford 0.130 g (53%) of the desired product as a solid.

EXAMPLE 19A



Preparation of 2R-hydroxy-3-[[(3-aminophenyl) sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl) propylamine

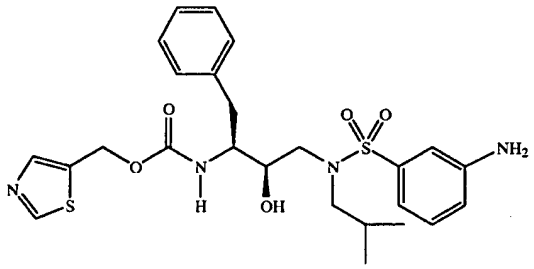
Part A: Preparation of Carbamic acid, [2R-hydroxy-3-[(3-nitrophenylsulfonyl)(2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, phenylmethyl ester

To a solution of 1.1 g (3.0 mmol) of N-[3S-benzyloxy carbonylamino-2R-hydroxy-4-phenyl]-N-isobutylamine in 15 mL of anhydrous methylene chloride, was added 1.3 mL (0.94 g, 9.3 mmol) of triethylamine. The solution was cooled to 0° C. and 0.67 g (3.0 mmol) of 3-nitrobenzene sulfonyl chloride was added, stirred for 30 minutes at 0° C., then for 1 hour at room temperature. Ethyl acetate was added, washed with 5% citric acid, saturated sodium bicarbonate, brine, dried and concentrated to yield 1.74 g of crude material. This was recrystallized from ethyl acetate/hexane to afford 1.40 g of pure carbamic acid, [2R-hydroxy-3-[(3-nitrophenylsulfonyl)(2-methylpropyl) amino]-1S-(phenylmethyl)propyl-, phenylmethyl ester, m/e=562(M+Li).

Part B: Preparation of [2R-hydroxy-3-[[(3-aminophenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propylamine

A solution of 1.33 g (2.5 mmol) of carbamic acid, [2R-hydroxy-3-[(3-nitrophenylsulfonyl)(2-methylpropyl) amino]-1S-(phenylmethyl)propyl-, phenylmethyl ester in 40 mL of 1:1 methanol/tetrahydrofuran was hydrogenated over 0.70 g of 10% palladium-on-carbon catalyst under 40 psig of hydrogen for 1.5 hours. The catalyst was removed by filtration and the solution concentrated to afford 0.87 g of the desired [2R-hydroxy-3-[[(3-aminophenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propylamine.

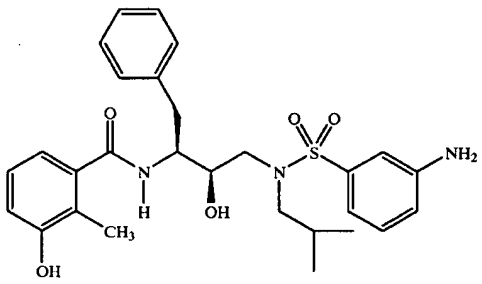
EXAMPLE 19B



Preparation of Carbamic acid, 2R-hydroxy-3-[[(3-aminophenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, 5-thiazolylmethyl ester

To a solution of 133 mg (1.15 mmol) of 5-(hydroxymethyl) thiazole in 3 mL of anhydrous acetonitrile, was added 0.30 mL (0.29 g, 3.7 mmol) of pyridine and then 296 mg (1.15 mmol) of N,N'-disuccinimidyl carbonate at room temperature under nitrogen. After 60 minutes, 460 mg (1.18 mmol) of 2R-hydroxy-3-[(2-methylpropyl)(3-aminophenyl)sulfonyl]amino-1S-(phenylmethyl)propylamine was added. After stirring at room temperature for 15 hours, ethyl acetate was added, washed with 5% citric acid, saturated sodium bicarbonate and brine, dried over magnesium sulfate, filtered and concentrated to afford 480 mg of crude product. This was chromatographed on silica gel using 50–80% ethyl acetate/hexane as eluent to afford 422 mg of a white solid, which was identified as the desired carbamic acid, 2R-hydroxy-3-[(3-aminophenyl sulfonyl)(2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, 5-thiazolylmethyl ester, m/e=539 (M+Li).

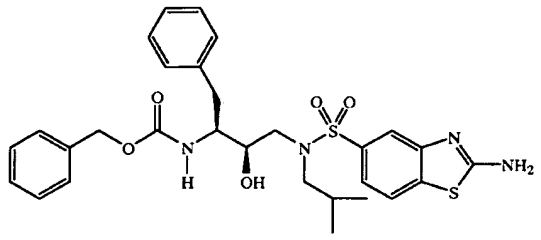
EXAMPLE 19C



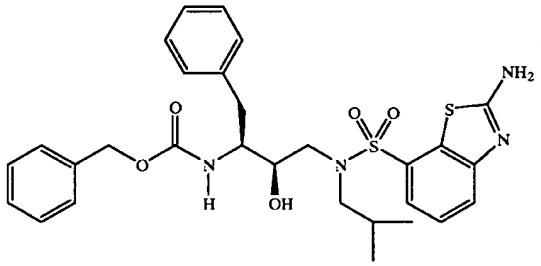
Preparation of Benzamide, N-[2R-hydroxy-3-[[(3-aminophenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-3-hydroxy-2-methyl

To a solution of 134 mg (0.88 mmol) of 3-hydroxy-2-methylbenzoic acid and 155 mg (1.15 mmol) of N-hydroxybenzotriazole in 5 mL of anhydrous N,N-dimethylformamide at 0° C., was added 167 mg (0.88 mmol) of EDC. After 20 minutes of activation at 0° C. and 1 hour at room temperature, 300 mg (1.0 mmol) of 2R-hydroxy-3-[(2-is methylpropyl)(3-aminophenyl)sulfonyl]amino-1S-(phenylmethyl)propylamine was added. After 15 hours at room temperature, ethyl acetate was added, washed with 5% citric acid, saturated sodium bicarbonate, brine, dried, filtered and concentrated to afford 330 mg of crude material. This was chromatographed on silica gel using 30–70% ethyl acetate/methylene chloride as eluent to afford 230 mg of pure benzamide, N-[2R-hydroxy-3-[[(3-aminophenyl) sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl) propyl]-3-hydroxy-2-methyl.

EXAMPLE 19D



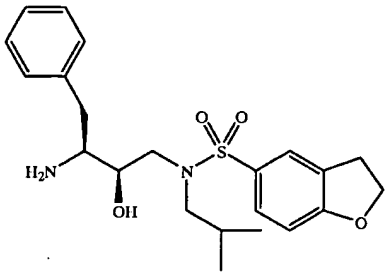
and



Preparation of Carbamic acid, 2R-hydroxy-3-[[(2-amino benzothiazol-5-yl)sulfonyl](2-methylpropyl) amino]-1S-(phenylmethyl)propyl-, phenylmethyl ester; and Carbamic acid, 2R-hydroxy-3-[[(2-aminobenzothiazol-7-yl)sulfonyl](2-methylpropyl) amino]-1S-(phenylmethyl)propyl-, phenylmethyl ester

The carbamic acid, 2R-hydroxy-3-[(3-aminophenylsulfonyl) (2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, phenylmethyl ester 0.36 g (0.685 mmol) was added to a well mixed powder of anhydrous copper sulfate (1.44 g) and potassium thiocyanate (1.80 g) followed by dry methanol (10 mL) and the rsulting black-brown suspension was heated at reflux for 2 hrs. The reaction mixture was filtered and the filtrate was diluted with water (5 mL) and heated at reflux. Ethanol was added to the reaction mixture, cooled and filtered. The filtrate upon concentration afforded a rseidue which was chromatographed (ethyl acetate:hexane 1:1) to afford 0.18 g (45%) of the 7-isomer as a solid. Further elution of the column with (ethyl acetate:hexane 3:2) afforded 0.80 g (20%) afforded the 5-isomer-as a solid.

EXAMPLE 20A



Preparation of 2R-hydroxy-3-[[(2,3-dihydrobenzofuran-5-yl)sulfonyl](2-methylpropyl) amino]-1S-(phenylmethyl) propylamine

Part A: Preparation of 5-(2,3-dihydrobenzofuranyl) sulfonyl chloride

To a solution of 3.35 g of anhydrous N,N-dimethylformamide at 0° C. under nitrogen was added 6.18 g of sulfuryl chloride, whereupon a solid formed. After stirring for 15 minutes, 4.69 g of 2,3-dihydrobenzofuran was added, and the mixture heated at 100° C. for 2 hours. The reaction was cooled, poured into ice water, extracted with methylene chloride, dried over magnesium sulfate, filtered and concentrated the crude material. This was recrystallized from ethyl acetate to afford 2.45 g of 5-(2,3-dihydrobenzofuranyl)sulfonyl chloride.

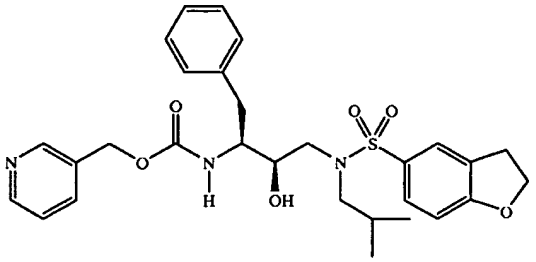
Part B: Preparation of Carbamic acid, 2R-hydroxy-3-[[(2,3-dihydrobenzofuran-5-yl)sulfonyl](2-methylpropyl) amino]-1S-(phenylmethyl)propyl-, phenylmethyl ester

To a solution of 1.11 g (3.0 mmol) of N-[3S-benzyloxy carbonylamino-2R-hydroxy-4-phenyl]-N-isobutylamine in 20 mL of anhydrous methylene chloride, was added 1.3 mL (0.94 g, 9.3 mmol) of triethylamine. The solution was cooled to 0° C. and 0.66 g of 5-(2,3-dihydrobenzofuranyl) sulfonyl chloride was added, stirred for 15 minutes at 0° C., then for 2 hour at room temperature. Ethyl acetate was added, washed with 5% citric acid, saturated sodium bicarbonate, brine, dried and concentrated to yield 1.62 g of crude material. This was recrystallized from diethyl ether to afford 1.17 g of pure carbamic acid, [2R-hydroxy-3-[[(2,3-dihydrobenzofuran-5-yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl) propyl-, phenylmethyl ester.

Part C: Preparation of [2R-hydroxy-3-[[(2,3-dihydro benzofuran-5-yl)sulfonyl](2-methylpropyl) amino]-1S-(phenylmethyl)propylamine

A solution of 2.86 g of carbamic acid, [2R-hydroxy-3-[[(2,3-dihydrobenzofuran-5-yl)sulfonyl](2-methylpropyl) amino]-1S-(phenylmethyl)propyl-, phenylmethyl ester in 30 mL of tetrahydrofuran was hydrogenated 0.99 g of 10% palladium-on-carbon under 50 psig of hydrogen for 16 hours. The catalyst was removed by filtration and the filtrate concentrated to afford 1.99 g of the desired [2R-hydroxy-3-[[(2,3-dihydrobenzofuran-5-yl)sulfonyl](2-methylpropyl) amino]-1S-(phenylmethyl) propylamine.

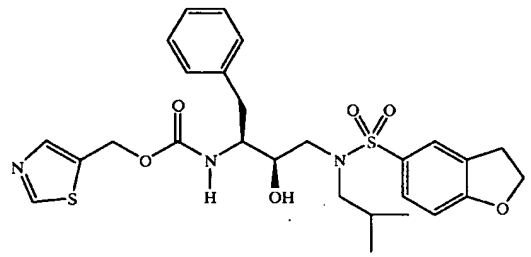
EXAMPLE 20B



Preparation of Carbamic acid, [2R-hydroxy-3-[[(2,3-dihydrobenzofuran-5-yl)sulfonyl](2-methylpropyl) amino]-1S-(phenylmethyl)propyl-, 3-pyridylmethyl ester

To a solution of 110 mg of 3-pyridylcarbinol in 3 mL of anhydrous acetonitrile, was added 0.24 g of anhydrous pyridine and then 260 mg of N,N'disuccinimidyl carbonate at room temperature under nitrogen. After 45 minutes, 420 mg of 2R-hydroxy-3-[(2-methylpropyl)(2,3-dihydrobenzofuran-5-yl)sulfonyl]amino-1S-(phenylmethyl) propylamine was added. After stirring at room temperature for 20 hours, ethyl acetate was added, washed with 5% citric acid, saturated sodium bicarbonate and brine, dried over magnesium sulfate, filtered and concentrated to afford 320 mg of crude product. This was chromatographed on silica gel using 50% ethyl acetate/hexane as eluent to afford 260 mg of a white solid, which was identified as the desired carbamic acid, [2R-hydroxy-3-[[(2,3-dihydrobenzofuran-5-yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl) propyl-, 3-pyridylmethyl ester.

EXAMPLE 20C

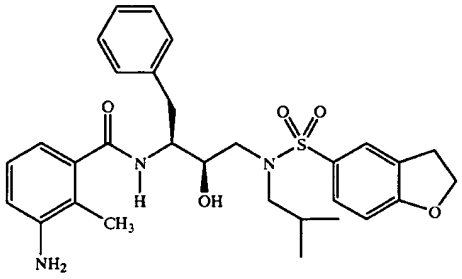


Preparation of Carbamic acid, [2R-hydroxy-3-[[(2,3-dihydrobenzofuran-5-yl)sulfonyl](2-methylpropyl) amino]-1S-(phenylmethyl)propyl-, 5-thiazolylmethyl ester

To a solution of 66 mg of 5-(hydroxymethyl)thiazole in 3 mL of anhydrous acetonitrile, was added 0.14 g of anhydrous pyridine and then 150 mg of N,N'-disuccinimidyl carbonate at room temperature under nitrogen. After 45 minutes, 240 mg of 2R-hydroxy-3-[(2-methylpropyl)(2,3-dihydrobenzofuran-5-yl)sulfonyl]amino-1S-(phenylmethyl) propylamine was added. After stirring at room temperature for 20 hours, ethyl acetate was added, washed with 5% citric acid, saturated sodium bicarbonate and brine, dried over magnesium sulfate, filtered and concentrated to afford 220 mg of crude product. This was chromatographed on silica

gel using 50% ethyl acetate/hexane as eluent to afford 120 mg of a white solid, which was identified as the desired carbamic acid, [2R-hydroxy-3-[[(2,3-dihydrobenzofuran-5-yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl) propyl-, 5-thiazolylmethyl ester.

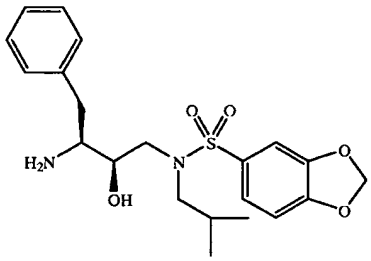
EXAMPLE 20D



Preparation of Benzamide, N-[2R-hydroxy-3-[[(2,3-dihydrobenzofuran-5-yl)sulfonyl](2-methylpropyl) amino]-1S-(phenylmethyl)propyl]-3-amino-2-methyl

To a solution of 175 mg of 3-amino-2-methylbenzoic acid in 2 mL of anhydrous N,N-dimethylformamide at 0° C., was added 200 mg of N-hydroxybenzotriazole and then 210 mg of EDC. After 20 minutes of activation, 405 mg of 2R-hydroxy-3-[[(2,3-dihydrobenzofuran-5-yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propylamine was added. After stirring at room temperature for 16 hours, ethyl acetate was added, wshed with 5% citric acid, sodium bicarbonate, brine, dried over magnesium sulfate, filtered and concentrated to afford 225 mg of crude product. This was chromatographed on silica gel using 50% ethyl acetate/hexane to afford 140 mg of the desired benzamide, N-[2R-hydroxy-3-[[(2,3-dihydrobenzofuran-5-yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl) propyl]-3-amino-2-methyl, m/e=552(M+H).

EXAMPLE 21A



Preparation of 2R-hydroxy-3-[[(1,3-benzodioxol-5-yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl) propylamine

Part A: Preparation of (1,3-Benzodioxol-5-yl) sulfonyl chloride

To a solution of 4.25 g of anhydrous N,N-dimethylformamide at 0° C. under nitrogen was added 7.84 g of sulfuryl chloride, whereupon a solid formed. After stirring for 15 minutes, 6.45 g of 1,3-benzodioxole was added, and the mixture heated at 100° C. for 2 hours. The reaction was cooled, poured into ice water, extracted with methylene chloride, dried over magnesium sulfate, filtered and concentrated to give 7.32 g of crude material as a black oil. This was chromatographed on silica gel using 20% methylene chloride/hexane to afford 1.9 g of (1,3-benzodioxol-5-yl)sulfonyl chloride.

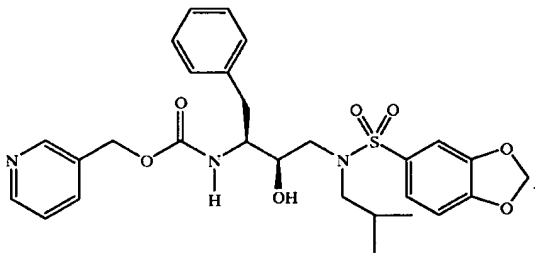
Part B: Preparation of Carbamic acid, 2R-hydroxy-3-[[(1,3-benzodioxol-5-yl)sulfonyl](2-methylpropyl) amino]-1S-(phenylmethyl)propyl-, phenylmethyl ester

To a solution of 3.19 g (8.6 mmol) of N-[3S-benzyloxy carbonylamino-2R-hydroxy-4-phenyl]-N-isobutylamine in 40 mL of anhydrous methylene chloride, was added 0.87 g of triethylamine. The solution was cooled to 0° C. and 1.90 g of (1,3-benzodioxol-5-yl)sulfonyl chloride was added, stirred for 15 minutes at 0° C., then for 17 hours at room temperature. Ethyl acetate was added, washed with 5% citric acid, saturated sodium bicarbonate, brine, dried and concentrated to yield crude material. This was recrystallized from diethyl ether/hexane to afford 4.77 g of pure carbamic acid, 2R-hydroxy-3-[[(1,3-benzodioxol-5-yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, phenylmethyl ester.

Part C: Preparation of 2R-hydroxy-3-[[(1,3-benzodioxol-5-yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propylamine

A solution of 4.11 g of carbamic acid, 2R-hydroxy-3-[[(1,3-benzodioxol-5-yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, phenylmethyl ester in 45 mL of tetrahydrofuran and 25 mL of methanol was hydrogenated over 1.1 g of 10% palladium-on-carbon under 50 psig of hydrogen for 16 hours. The catalyst was removed by filtration and the filtrate concentrated to afford 1.82 g of the desired 2R-hydroxy-3-[[(1,3-benzodioxol-5-yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propylamine.

EXAMPLE 21B

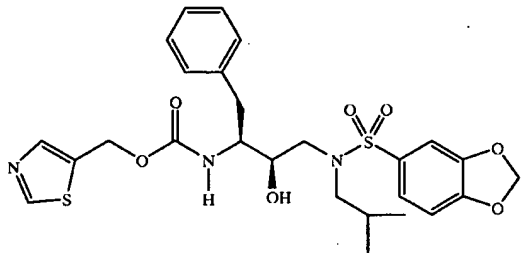


Preparation of Carbamic acid, 2R-hydroxy-3-[[(1,3-benzodioxol-5-yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, 3-pyridylmethyl ester

To a solution of 110 mg of 3-pyridylcarbinol in 3 mL of anhydrous acetonitrile, was added 0.24 g of anhydrous pyridine and then 260 mg of N,N'disuccinimidyl carbonate at room temperature under nitrogen. After 45 minutes, 410 mg of 2R-hydroxy-3-[[(1,3-benzodioxol-5-yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propylamine was added. After stirring at room temperature for 20 hours, ethyl acetate was added, washed with 5% citric acid, saturated sodium bicarbonate and brine, dried over magnesium sulfate, filtered and concentrated to afford 330 mg of crude

product. This was chromatographed on silica gel using 50% ethyl acetate/hexane as eluent to afford 160 mg of a white solid, which was identified as the desired carbamic acid, [2R-hydroxy-3-[[(1,3-benzodioxol-5-yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, 3-pyridylmethyl ester, m/e=562(M+Li).

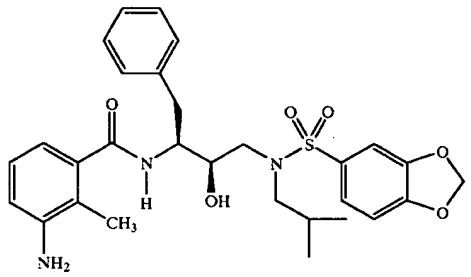
EXAMPLE 21C



Preparation of Carbamic acid, 2R-hydroxy-3-[[(1,3-benzodioxol-5-yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, 5-thiazolylmethyl ester

To a solution of 85 mg (0.8 mmol) of 5-(hydroxymethyl) thiazole in 2.2 mL of anhydrous acetonitrile, was added 0.18 mL (2.2 mmol) of anhydrous pyridine and then 189 mg (0.74 mmol) of N,N'-disuccinimidyl carbonate at room temperature under nitrogen. After 45 minutes, 310 mg of 2R-hydroxy-3-[[(1,3-benzodioxol-5-yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propylamine was added. After stirring at room temperature for 20 hours, ethyl acetate was added, washed with 5% citric acid, saturated sodium bicarbonate and brine, dried over magnesium sulfate, filtered and concentrated to afford 300 mg of crude product. This was chromatographed on silica gel using 50% ethyl acetate/hexane as eluent to afford 150 mg of a white solid, which was identified as the desired carbamic acid, 2R-hydroxy-3-[[(1,3-benzodioxol-5-yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, 5-thiazolylmethyl ester, m/e=568(M+Li).

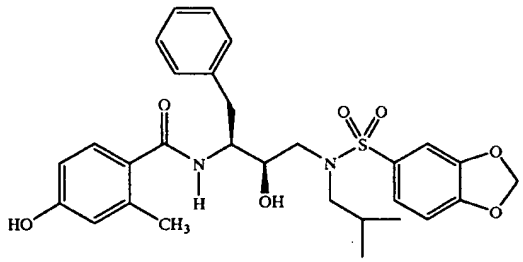
EXAMPLE 21D



Preparation of Benzamide, N-[2R-hydroxy-3-[[(1,3-benzodioxol-5-yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-3-amino-2-methyl

To a solution of 175 mg of 3-amino-2-methylbenzoic acid in 2 mL of anhydrous N,N-dimethylformamide at 0° C., was added 200 mg of N-hydroxybenzotriazole and then 210 mg of EDC. After 20 minutes of activation, 410 mg of 2R-hydroxy-3-[[(1,3-benzodioxol-5-yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propylamine was added. After stirring at room temperature for 16 hours, ethyl acetate was added, washed with 5% citric acid, sodium bicarbonate, brine, dried over magnesium sulfate, filtered and concentrated to afford 500 mg of crude product. This was chromatographed on silica gel using 50% ethyl acetate/hexane to afford 310 mg of the desired benzamide, N-[2R-hydroxy-3-[[(1,3-benzodioxol-5-yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-3-amino-2-methyl, m/e=560(M+Li).

EXAMPLE 21E



Preparation of Benzamide, N-[2R-hydroxy-3-[[(1,3-benzodioxol-5-yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-4-hydroxy-2-methyl

Part A: Preparation of 2-Trimethylsilyloxy-1,3-cyclohexadiene

A 100 mL round bottom flask equipped with magnetic stir bar, addition funnel, and N_2 inlet was charged with 40 mL dry THF and 8.3 mL diisopropyl amine. The solution was cooled to −78° C. and charged with 23.8 mL of 2.5M nBuLi in Hexane. After 10 minutes a solution of 5.2 g cyclohexenone in 10 mL THF was added dropwise. The reaction was stirred 10 minutes at −78° C. and quenched with 7.5 mL trimethylsilyl chloride. The reaction was stirred 15 minutes and then partitioned between diethyl ether and cold saturated aqueous sodium bicarbonate. The combined organic layers were dried over sodium sulfate and concentrated in vacuo to a yellow oil. Short path distillation (BP 27–29° C./0.5 mm) afforded 6.0 g (66%) of 2-Trimethylsilyloxy-1,3-Cyclohexadiene.

Part B: Preparation of Methyl (2-methyl-4-trimethylsilyoxy)benzoate

A 50 mL round bottom flask equipped with magnetic stir bar and condenser was charged with 6.0 g of 2-trimethylsilyloxy-1,3-cyclohexadiene, 3.5 g methyl tetrolate in 3 mL dry toluene. The reaction was heated to 150° C. for 50 hours at which point ^{1}H-NMR indicated no starting diene. The raction was concentrated in vacuo to provide 5.7 g (67%) methyl 2-methyl-4-trimethylsilyloxybenzoate.

Part C: Preparation of 4-Hydroxy-2-methylbenzoic acid

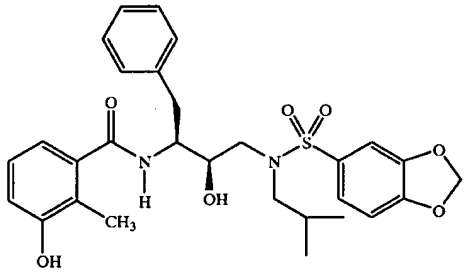
A 100 mL round bottom flask equipped with magnetic stir bar was charged with 5.7 g methyl 2-methyl-4-trimethylsilyloxybenzoate and 2.0 g LiOH in 40 mL methanol and 10 mL water. After 2 hours at reflux the reaction was poured into 10 mL concentrated HCl and then 100 g ice. Extraction with ethyl acetate followed by concentration in vacuo gave a crude solid (70:30) product:starting material.

Flash Chromatography using 50-50 ethyl acetate/hexanes as an eluent gave 1.15 g 2-methyl-4-hydroxybenzoic acid, m/e=193(M+H).

Part D: Preparation of Benzamide, N-[2R-hydroxy-3-[[(1,3-benzodioxol-5-yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-4-hydroxy-2-methyl

To a solution of 175 mg of 4-hydroxy-2-methylbenzoic acid in 2 mL of anhydrous N,N-dimethylformamide at 0° C., was added 200 mg of N-hydroxybenzotriazole and then 220 mg of EDC. After 20 minutes of activation, 450 mg of 2R-hydroxy-3-[[(1,3-benzodioxol-5-yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propylamine was added. After stirring at room temperature for 16 hours, ethyl acetate was added, washed with 5% citric acid, sodium bicarbonate, brine, dried over magnesium sulfate, filtered and concentrated to afford crude product. This was chromatographed on silica gel using 50% ethyl acetate/hexane to afford 102 mg of the desired benzamide, N-[2R-hydroxy-3-[[(1,3-benzodioxol-5-yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-4-hydroxy-2-methyl.

EXAMPLE 21F



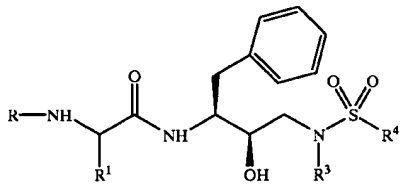
Preparation of Benzamide, N-[2R-hydroxy-3-[[(1,3-benzodioxol-5-yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-3-hydroxy-2-methyl

To a solution of 187 mg (1.23 mmol) of 3-hydroxy-2-methylbenzoic acid and 217 mg (1.61 mmol) of N-hydroxybenzotriazole in 6 mL of anhydrous N,N-dimethylformamide at 0° C., was added 236 mg (1.23 mmol) of EDC. After 20 minutes of activation at 0° C. and 1 hour at room temperature, 450 mg (1.07 mmol) of 2R-hydroxy-3-[[(1,3-benzodioxol-5-yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propylamine was added. After 15 hours at room temperature, ethyl acetate was added, washed with 5% citric acid, saturated sodium bicarbonate, brine, dried, filtered and concentrated to afford 650 mg of crude material. This was chromatographed on silica gel using 0–25% ethyl acetate/methylene chloride as eluent to afford 390 mg of pure benzamide, N-[2R-hydroxy-3-[[(1,3-benzodioxol-5-yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-3-hydroxy-2-methyl, m/e=561(M+Li).

EXAMPLE 22

Following the procedures of Examples 1–21, the compounds shown in Tables 3, 5A and 5B were prepared and in Tables 4 through 17 can be prepared.

TABLE 3



Entry No.	R	R^1	R^3	R^4
1	Cbz	t-Butyl	i-Amyl	Methyl
2	N,N-Dimethylglycine	t-Butyl	i-Amyl	Methyl
3	Cbz	i-Propyl	i-Amyl	Phenyl
4	Cbz	sec-Butyl	i-Amyl	Phenyl
5	Cbz	$CH_2C(O)NH_2$	n-Propyl	Phenyl
6	N-Methylglycine	t-Butyl	i-Amyl	Phenyl
7	Cbz	t-Butyl	i-Butyl	Phenyl
8	N,N-Dimethylglycine	t-Butyl	i-Amyl	Phenyl
9	N-Methylglycine	t-Butyl	i-Amyl	Phenyl
10	N,N-Dimethylglycine	t-Butyl	i-Butyl	(4-OCH_3)Phenyl
11	N-Methylglycine	t-Butyl	i-Butyl	(4-OCH_3)Phenyl

TABLE 4

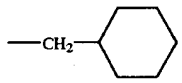
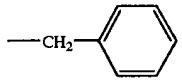
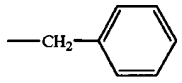
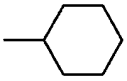
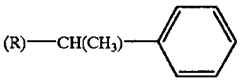
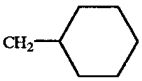
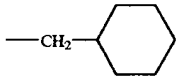
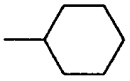
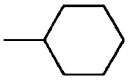
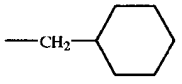
Entry	No. R	R^3	R^4
1	Cbz[a]	CH_3	n-Butyl
2	Cbz	i-Butyl	CH_3
3	Cbz	i-Butyl	n-Butyl
4	Q[b]	i-Butyl	n-Butyl
5	Cbz	i-Propyl	n-Butyl
6	Q	i-Propyl	n-Butyl
7	Cbz	C_6H_5	n-Butyl
8	Cbz		n-Butyl
9	Cbz		n-Butyl
10	Q		n-Butyl
11	Cbz		n-Butyl
12	Cbz	i-Butyl	n-Propyl
13	Cbz	i-Butyl	$-CH_2CH(CH_3)_2$
14	Cbz		n-Butyl
15	Cbz		i-Propyl
16	Cbz		$-CH_2CH_2CH(CH_3)_2$
17	Cbz	i-Butyl	$-CH_2CH_3$
18	Cbz	i-Butyl	$-CH(CH_3)_2$
19	Cbz	i-Butyl	
20	Q	-Butyl	
21	Cbz		$-(CH_2)_2CH(CH_3)_2$
22	Cbz	$(CH_2)_2CH(CH_3)_2$	$-CH(CH_3)_2$
23	Q	i-Butyl	$-CH(CH_3)_2$
24	Cbz	i-Butyl	$-C(CH_3)_3$
25	Q	i-Butyl	$-C(CH_3)_3$

TABLE 4-continued

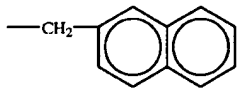
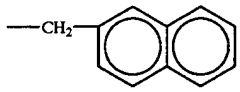
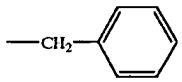
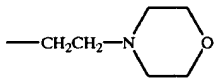
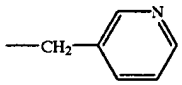
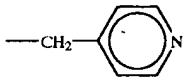
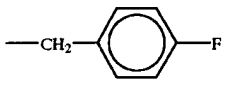
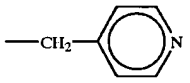
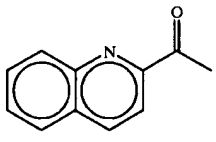
Entry	No. R	R^3	R^4
26	Cbz		$-C(CH_3)_3$
27	Q		$-C(CH_3)_3$
28	Cbz	$-(CH_2)_2CH(CH_3)_2$	$-C(CH_3)_3$
29	Q	$-(CH_2)_2CH(CH_3)_2$	$-C(CH_3)_3$
30	Cbz	$-CH_2C6H_5$	$-C(CH_3)_3$
31	Q	$-CH_2C_6H_5$	$-C(CH_3)_3$
32	Cbz	$-(CH_2)_2C_6H_5$	$-C(CH_3)_3$
33	Cbz	$-(CH_2)_2C_6H_5$	$-C(CH_3)_3$
34	Cbz	n-Butyl	$-C(CH_3)_3$
35	Cbz	n-Pentyl	$-C(CH_3)_3$
36	Cbz	n-Hexyl	$-C(CH_3)_3$
37	Cbz		$-C(CH_3)_3$
38	Cbz	$-CH_2C(CH_3)_3$	$-C(CH_3)_3$
39	Q	$-CH_2C(CH_3)_3$	$-C(CH_3)_3$
40	Cbz		$-C(CH_3)_3$
41	Cbz	$-CH_2C_6H_5OCH_3$(para)	$-C(CH_3)_3$
42	Cbz		$-C(CH_3)_3$
43	Cbz		$-C(CH_3)_3$
44	Cbz	$-(CH_2)_2C(CH_3)_3$	$-C(CH_3)_3$
45	Q	$-(CH_2)_2C(CH_3)_3$	$-C(CH_3)_3$
46	Cbz	$-(CH_2)_4OH$	$-C(CH_3)_3$
47	Q	$-(CH_2)_4OH$	$-C(CH_3)_3$
48	Q		$-C(CH_3)_3$
49	Q		$-C(CH_3)_3$
50	Cbz	$-CH_2CH(CH_3)_2$	$-C_6H_5$
51		$-CH_2CH(CH_3)_2$	$-C_6H_5$

TABLE 4-continued

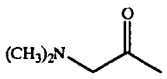
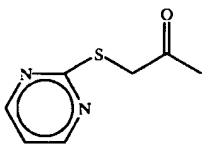
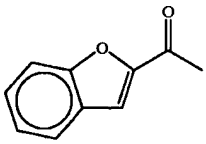
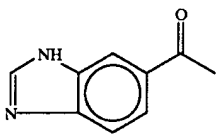
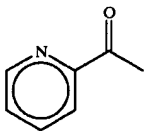
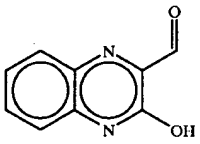
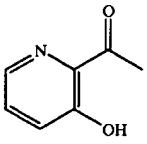
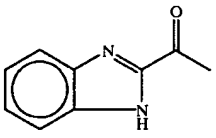
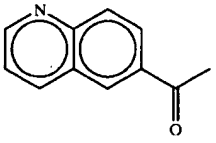
Entry	No. R	R^3	R^4
52		$-CH_2CH(CH_3)_2$	$-C_6H_5$
53		$-CH_2CH(CH_3)_2$	$-C_6H_5$
54		$-CH_2CH(CH_3)_2$	$-C_6H_5$
55		$-CH_2CH(CH_3)_2$	$-C_6H_5$
56		$-CH_2CH(CH_3)_2$	$-C_6H_5$
57		$-CH_2CH(CH_3)_2$	$-C_6H_5$
58		$-CH_2CH(CH_3)_2$	$-C_6H_5$
59		$-CH_2CH(CH_3)_2$	$-C_6H_5$
60		$-CH_2CH(CH_3)_2$	$-C_6H_5$
61		$-CH_2CH(CH_3)_2$	$-C_6H_5$

TABLE 4-continued

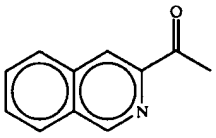
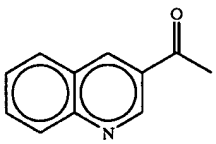
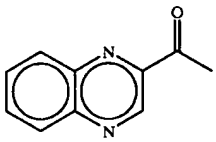
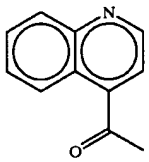
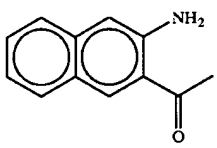
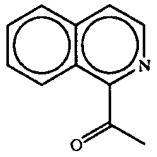
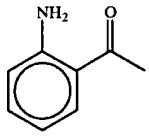
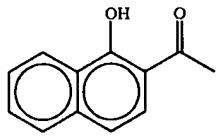
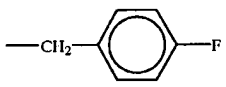
Entry	No. R	R^3	R^4
62		$-CH_2CH(CH_3)_2$	$-C_6H_5$
63		$-CH_2CH(CH_3)_2$	$-C_6H_5$
64		$-CH_2CH(CH_3)_2$	$-C_6H_5$
65		$-CH_2CH(CH_3)_2$	$-C_6H_5$
66		$-CH_2CH(CH_3)_2$	$-C_6H_5$
67		$-CH_2CH(CH_3)_2$	$-C_6H_5$
68		$-CH_2CH(CH_3)_2$	$-C_6H_5$
69		$-CH_2CH(CH_3)_2$	$-C_6H_5$
70	Q	$-CH_2Ph$	$-Ph$
71	Q		$-Ph$

TABLE 4-continued

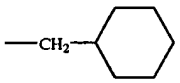
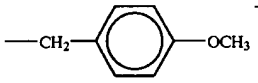
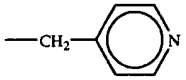
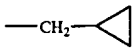
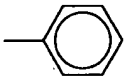
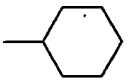
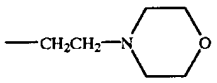
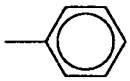
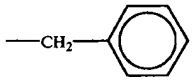
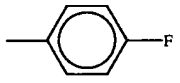
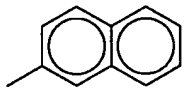
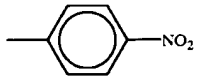
Entry	No. R	R^3	R^4
72	Q		—Ph
73	Q		—Ph
74	Q		—Ph
75	Q		—Ph
76	Q	—$CH_2CH{=}CH_2$	—Ph
77	Q		—Ph
78	Q		—Ph
79	Q	—CH_2CH_2Ph	—Ph
80	Q	—$CH_2CH_2CH_2CH_2OH$	—Ph
81	Q	—$CH_2CH_2N(CH_3)_2$	—Ph
82	Q		—Ph
83	Q	—CH_3	—Ph
84	Q	—$CH_2CH_2CH_2SCH_3$	—Ph
85	Q	—$CH_2CH_2CH_2S(O)_2CH_3$	—Ph
86	Q	—$CH_2CH_2CH_2CH(CH_3)_2$	
87	Q	—$CH_2CH_2CH(CH_3)_2$	
88	Q	—$CH_2CH_2CH(CH_3)_2$	—$CH_2CH_2CH_3$
89	Q	—$CH_2CH_2CH_2CH(CH_3)_2$	—CH_3
90	Q	—$CH_2CH_2CH(CH_3)_2$	
91	Q	—$CH_2CH_2CH(CH_3)_2$	
92	Q	—$CH_2CH_2CH(CH_3)_2$	

TABLE 4-continued

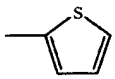
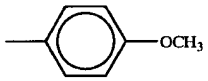
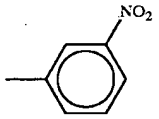
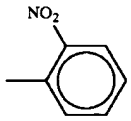
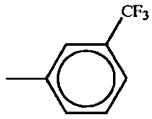
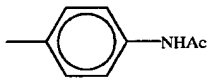
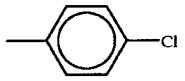
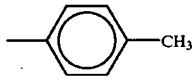
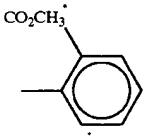
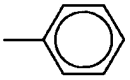
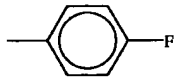
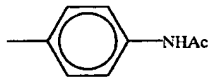
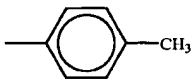
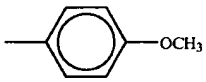
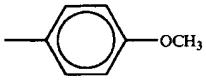
Entry	No. R	R^3	R^4
93	Q	$-CH_2CH_2CH(CH_3)_2$	
94	Q	$-CH_2CH_2CH(CH_3)_2$	
95	Q	$-CH_2CH_2CH(CH_3)_2$	
96	Q	$-CH_2CH_2CH(CH_3)_2$	
97	Q	$-CH_2CH_2CH(CH_3)_2$	
98	Q	$-CH_2CH_2CH(CH_3)_2$	
99	Q	$-CH_2CH_2CH(CH_3)_2$	
100	Q	$-CH_2CH_2CH(CH_3)_2$	
101	Q	$-CH_2CH_2CH(CH_3)_2$	
102	Q	$-CH_2CH_2CH(CH_3)_2$	
103	Q	$-CH_2CH(CH_3)_2$	
104	Q	$-CH_2CH(CH_3)_2$	

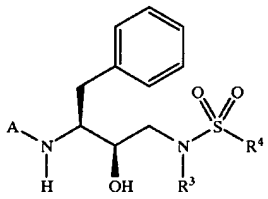
TABLE 4-continued

Entry	No. R	R^3	R^4
105	Q	$-CH_2CH(CH_3)_2$	
106	Q	$-CH_2CH_2CH_3$	
107	Q	$-CH_2CH_2CH_2CH_3$	

[a]benzyloxycarbonyl

[b]2-quinolinylcarbonyl

TABLE 5



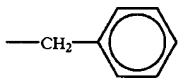
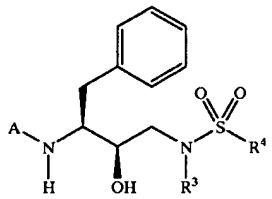
Entry	A	R^3	R^4
1	Cbz-Val	i-amyl	$-C_6H_5$
2	Cbz-Leu	i-amyl	$-C_6H_5$
3	Cbz-Ile	i-amyl	$-C_6H_5$
4	Ac-D-homo-Phe	i-Bu	methyl
5	Qui-Orn(g-Cbz)		$-C_6H_5$
6	Cbz-Asn	$-CH_2CH=CH_2$	$-C_6H_5$
7	Acetyl-t-BuGly	i-amyl	$-C_6H_5$
8	Acetyl-Phe	i-amyl	$-C_6H_5$
9	Acetyl-Ile	i-amyl	$-C_6H_5$
10	Acetyl-Leu	i-amyl	$-C_6H_5$
11	Acetyl-His	i-amyl	$-C_6H_5$
12	Acetyl-Thr	i-amyl	$-C_6H_5$
13	Acetyl-NHCH($C(CH_3)_2(SCH_3)$)C(O)—	i-amyl	$-C_6H_5$
14	Cbz-Asn	i-amyl	$-C_6H_5$
15	Cbz-Ala	i-amyl	$-C_6H_5$
16	(N,N-dimethylglycinyl)Val	i-amyl	$-C_6H_5$
17	(N-methylglycinyl)Val	i-amyl	$-C_6H_5$
18	(N,N-dimethylglycinyl)Ile	i-amyl	$-C_6H_5$
19	(N-methylglycinyl)Ile	i-amyl	$-C_6H_5$
20	Cbz-Ala	i-amyl	$-C_6H_5$
21	Cbz-beta-cyanoAla	i-amyl	$-C_6H_5$
22	Cbz-t-BuGly	i-amyl	$-C_6H_5$
23	Q-t-BuGly	i-amyl	$-C_6H_5$
24	Q-SCH_3Cys	i-amyl	$-C_6H_5$
25	Cbz-SCH_3Cys	i-amyl	$-C_6H_5$
26	Q-Asp	i-amyl	$-C_6H_5$
27	Cbz-(NHCH($C(CH_3)_2(SCH_3)$)C(O)—	i-amyl	$-C_6H_5$
28	Cbz-EtGly	i-amyl	$-C_6H_5$
29	Cbz-PrGly	i-amyl	$-C_6H_5$
30	Cbz-Thr	i-amyl	$-C_6H_5$
31	Q-Phe	i-amyl	$-C_6H_5$
32	Cbz-Phe	i-amyl	$-C_6H_5$

TABLE 5-continued



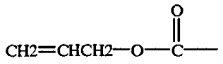
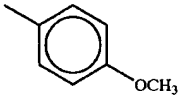
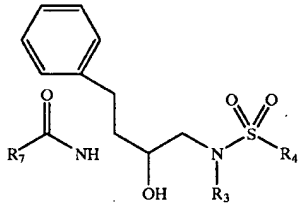
Entry	A	R^3	R^4
33		i-Butyl	—C_6H_4 

TABLE 5A



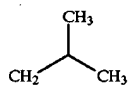
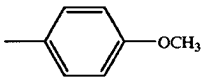
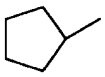
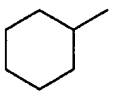
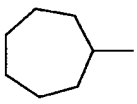
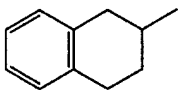
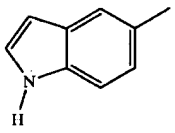
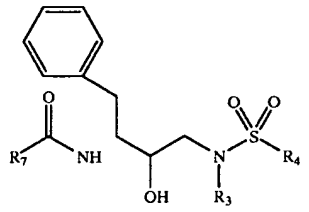
Entry	R^3	R^4	R^7	MASS MEASUREMENT MOL FORM	CALC M + H	FOUND
1				$C_{27}H_{38}N_2O_5S$	503.2661	503.2624
2				$C_{28}H_{40}N_2O_5S$	517.2736	517.2777
3				$C_{29}H_{42}N_2O_5S$	531.2893	531.2916
4				$C_{32}H_{40}N_2O_5S$	565.2736	565.2731
5				$C_{30}H_{35}N_3O_5S$	550.2376	550.2427

TABLE 5A-continued



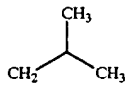
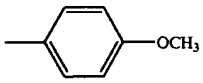
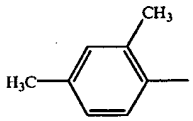
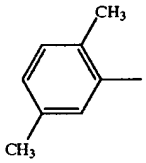
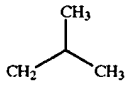
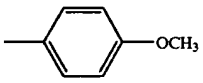
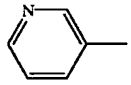
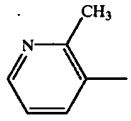
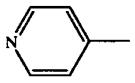
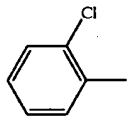
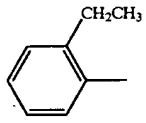
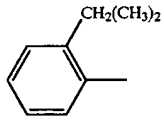
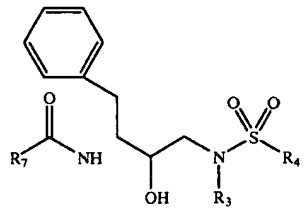
Entry	R^3	R^4	R^7	MASS MEASUREMENT MOL FORM	CALC M + H	FOUND
6				$C_{30}H_{38}N_2O_5S$	539 (M + H)	539
7				$C_{29}H_{36}N_2O_5S$	?	?
8				$C_{30}H_{38}N_2O_5S$	539.2580 (M + H)	539.2591
9				$C_{27}H_{33}N_3O_5S$	512.2219	512.2271
10				$C_{28}H_{35}N_3O_5S$	526.2376	526.2388
11				$C_{27}H_{33}N_3O_5S$	512.2219	512.2287
12				$C_{28}H_{33}N_2O_5ClS$	545.1877	545.1887
13				$C_{30}H_{38}N_2O_5S$	539.2580	539.2592
14				$C_{31}H_{40}N_2O_5S$	553.2736	553.2714

TABLE 5A-continued



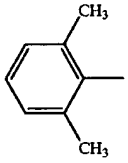
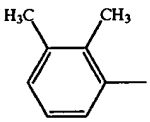
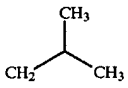
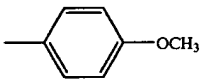
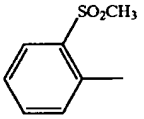
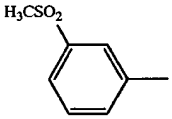
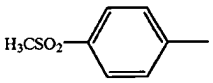
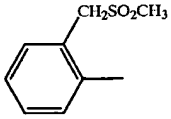
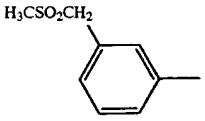
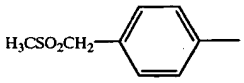
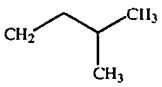
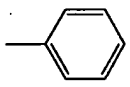
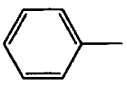
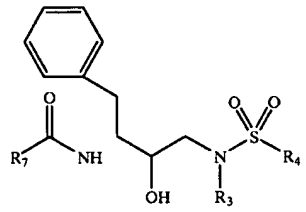
Entry	R^3	R^4	R^7	MASS MEASUREMENT MOL FORM	CALC M + H	FOUND
15				$C_{30}H_{38}N_2O_5S$	539.2580	539.2632
16				$C_{30}H_{38}N_2O_5S$	539 (M + H)	539
17				$C_{29}H_{36}N_2O_7S_2$	589.2042 (M + H)	589.2086
18				$C_{29}H_{36}N_2O_7S_2$	595.2124 (M + Li)	595.2103
19				$C_{29}H_{36}N_2O_7S_2$	595.2124 (M + Li)	595.2191
20				$C_{30}H_{38}N_2O_7S_2$	609.2281 (M + Li)	609.2313
21				$C_{30}H_{38}N_2O_7S_2$	603.2199 (M + H)	603.2247
22				$C_{30}H_{38}N_2O_7S_2$	603.2199 (M + H)	603.2266
23						

TABLE 5A-continued



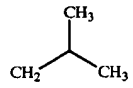
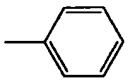
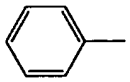
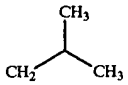
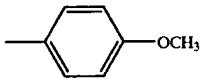
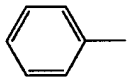
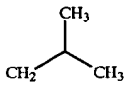
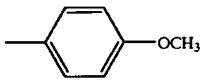
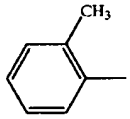
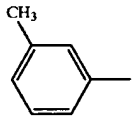
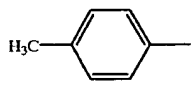
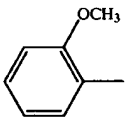
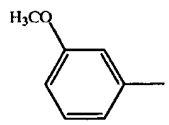
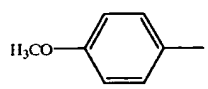
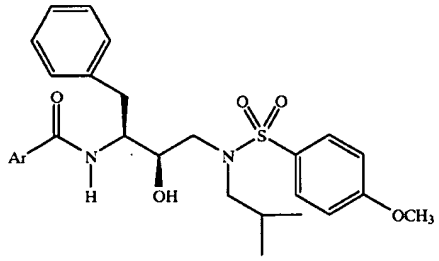
Entry	R^3	R^4	R^7	MASS MEASUREMENT MOL FORM	CALC M + H	FOUND
24				$C_{27}H_{32}N_2O_4S$	481.2161	481.2213
25				$C_{28}H_{35}N_2O_5S$	511.2267	511.2319
26				$C_{29}H_{36}N_2O_5S$	525.2423	525.2469
27				$C_{29}H_{36}N_2O_5S$	525.2428	525.2464
28				$C_{29}H_{36}N_2O_5S$	525.2423	525.2432
29				$C_{29}H_{36}N_2O_6S$	541.2372	541.2332
30				$C_{29}H_{36}N_2O_6S$	541.2372	541.2355
31				$C_{29}H_{36}N_2O_6S$	541.2372	541.2329

TABLE 5B



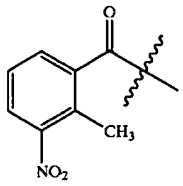
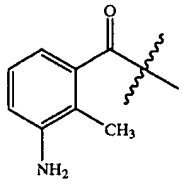
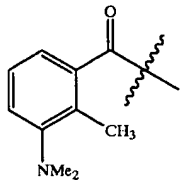
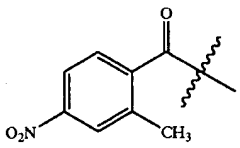
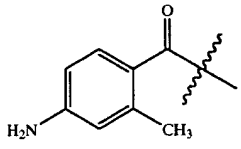
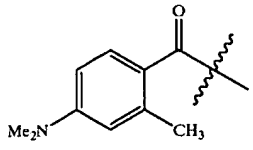
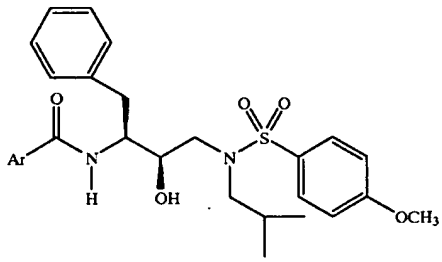
Entry A	Molecular Formula	Mass Spectrum
	$C_{29}H_{35}N_3O_7S$	576 (M + Li)
	$C_{29}H_{37}N_3O_5S$	540 (M + H)
	$C_{31}H_{41}N_3O_5S$	568 (M + H)
	$C_{29}H_{35}N_3O_7S$	570 (M + H)
	$C_{29}H_{37}N_3O_5S$	540 (M + H)
	$C_{31}H_{41}N_3O_5S$	568 (M + H)

TABLE 5B-continued



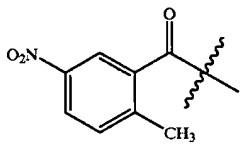
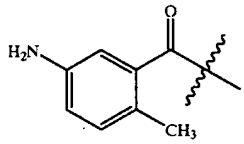
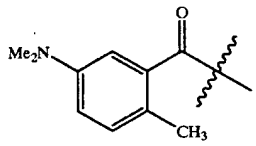
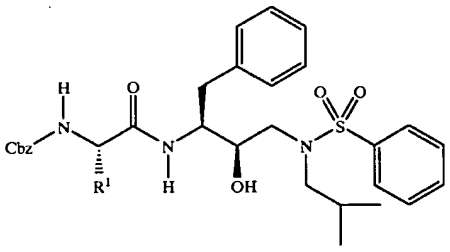
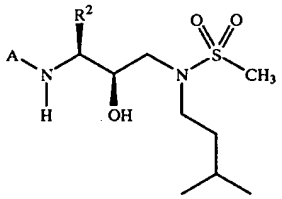
Entry A	Molecular Formula	Mass Spectrum
	$C_{29}H_{35}N_3O_7S$	570 (M + H)
	$C_{29}H_{37}N_3O_5S$	546 (M + Li)
	$C_{31}H_{41}N_3O_5S$	574 (M + Li)

TABLE 6



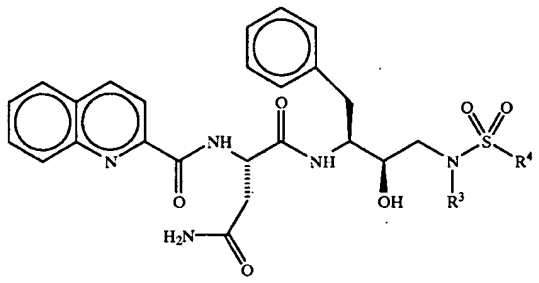
Entry	R^1
1	$CH_2SO_2CH_3$
2	(R)-$CH(OH)CH_3$
3	$CH(CH_3)_2$
4	(R, S)CH_2SOCH_3
5	$CH_2SO_2NH_2$
6	CH_2SCH_3
7	$CH_2CH(CH_3)_2$
8	$CH_2CH_2C(O)NH_2$
9	(S)-$CH(OH)CH_3$
10	$-CH_2C\equiv C-H$

TABLE 7



Entry	R^2	A
1	n-Bu	Cbz-Asn
2	cyclohexylmethyl	Cbz-Asn
3	n-Bu	Boc
4	n-Bu	Cbz
5	$C_6H_5CH_2$	Boc
6	P-F-$C_6H_5CH_2$	Cbz
7	$C_6H_5CH_2$	benzoyl
8	cyclohexylmethyl	Cbz
9	n-Bu	Q-Asn
10	cyclohexylmethyl	Q-Asn
11	$C_6H_5CH_2$	Cbz-Ile
12	$C_6H_5CH_2$	Q-Ile
13	P-F-$C_6H_5CH_2$	Cbz-t-BuGly
14	$C_6H_5CH_2$	Q-t-BuGly
15	$C_6H_5CH_2$	Cbz-Val
16	$C_6H_5CH_2$	Q-Val
17	2-naphthylmethyl	Cbz-Asn
18	2-naphthylmethyl	Q-Asn
19	2-naphthylmethyl	Cbz
20	n-Bu	Cbz-Val
21	n-Bu	Q-Val
22	n-Bu	Q-Ile
23	n-Bu	Cbz-t-BuGly
24	n-Bu	Q-t-BuGly
25	p-F(C_6H_4)CH_2	Q-Asn
26	p-F(C_6H_4)CH_2	Cbz
27	p-F(C_6H_4)CH_2	Cbz-Asn
28	$C_6H_5CH_2$	Cbz-propargylglycine
29	$C_6H_5CH_2$	Q-propargylglycine
30	$C_6H_5CH_2$	acetylpropargylglycine

TABLE 8



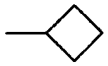
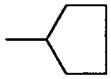
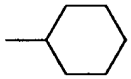
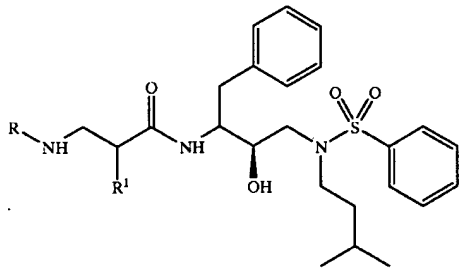
Entry	R^3	R^4
1	$-CH_2CH(CH_3)_2$	$-C(CH_3)_2$
2	$-CH_2CH_2CH(CH_3)_2$	
3	$-CH_2CH_2CH(CH_3)_2$	
4	$-CH_2CH_2CH(CH_3)_2$	
5	$-CH_2CH_2CH(CH_3)_2$	

TABLE 9



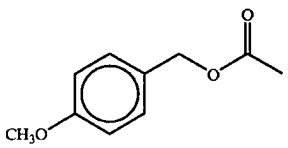
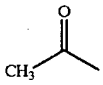
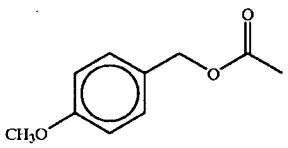
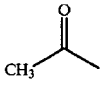
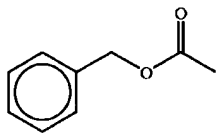
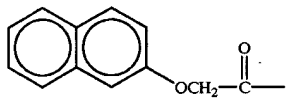
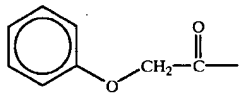
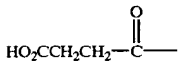
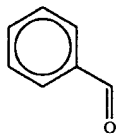
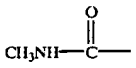
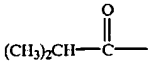
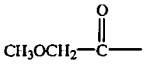
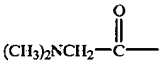
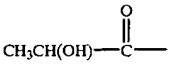
Entry	R	R^1
1		$-CH_3$
2		$-CH_3$
3		$-CH(CH_3)_2$
4		$-CH(CH_3)_2$
5		$-C(CH_3)_3$
6		$-CH_3$
7		$-CH_3$
8		$-CH_3$
9		$-CH_3$

TABLE 9-continued

10		—CH_3
11		—CH_3
12		—CH_3
13		—CH_3
14		—CH_3

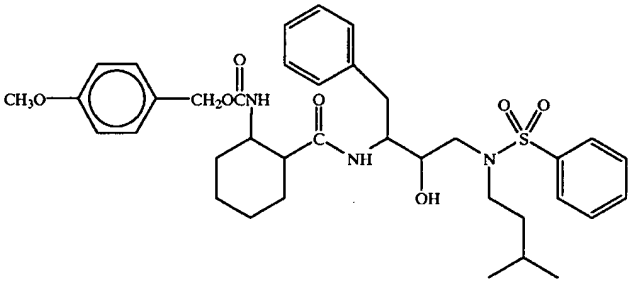
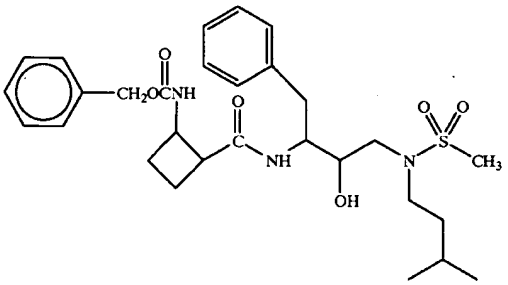
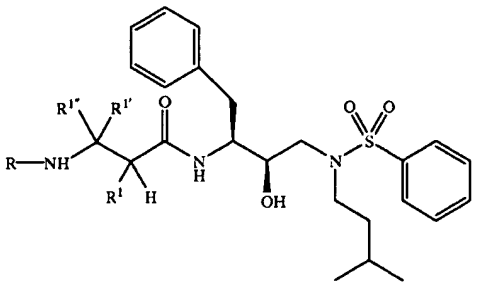
Entry	
15	
16	

TABLE 10



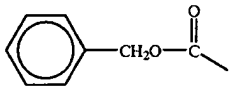
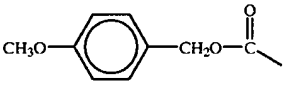
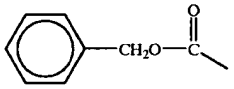
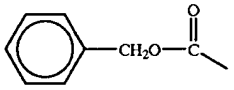
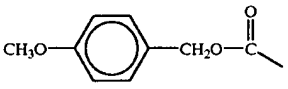
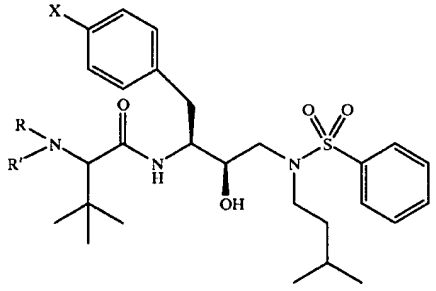
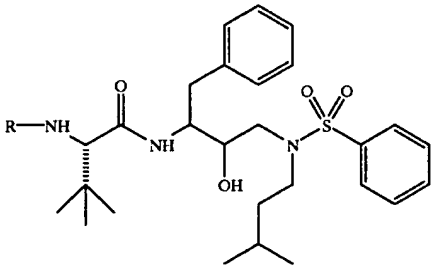
Entry	R^1	$R^{1'}$	$R^{1''}$	R
1	H	H	H	
2	H	H	H	
3	H	CH_3	H	
4	H	CH_3	CH_3	
5	H	H	CO_2CH_3	
6	H	H	H	
7	H	H	H	
8	H	H	$CONH_2$	Cbz
9	H	H	$CONH_2$	2-quinolinylcarbonyl

TABLE 11



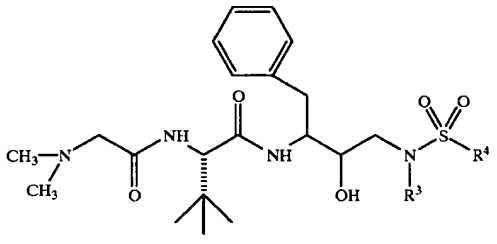
Entry	R	R'	X
1	R = H	R' = H	X = H
2	R = Me	R' = Me	X = H
3	R = H	R' = Me	X = H
4	R = Me	R' = Me	X = F
5	R = H	R' = Me	X = F
6	R = Cbz	R' = Me	X = H
7	R = H	R' = Bz	X = H
8	R + R' = pyrrole	X = H	

TABLE 12



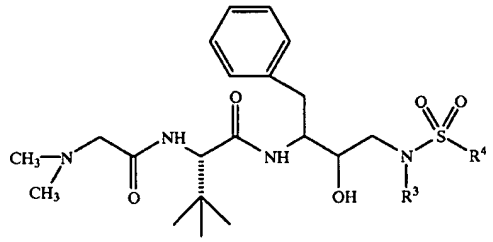
Entry	Acyl Group (R)
1	benzyloxycarbonyl
2	tert-butoxycarbonyl
3	acetyl
4	2-quinoylcarbonyl
5	phenoxyacetyl
6	benzoyl
7	methyloxaloyl
8	pivaloyl
9	trifluoracetyl
10	bromoacetyl
11	hydroxyacetyl
12	morpholinylacetyl
13	N,N-dimethylaminoacetyl
14	N-benzylaminoacetyl
15	N-phenylaminoacetyl
16	N-benzyl-N-methylaminoacetyl
17	N-methyl-N-(2-hydroxyethyl)aminoacetyl
18	N-methylcarbamoyl
19	3-methylbutyryl
20	N-isobutylcarbamoyl
21	succinoyl(3-carboxypropionyl)
22	carbamoyl
23	N-(2-indanyl)aminoacetyl

TABLE 13



Entry	R^3	R^4
1	$-CH_3$	—n-Butyl
2	—i-Butyl	$-CH_3$
3	—i-Butyl	—n-Butyl
4	—i-Propyl	—n-Butyl
5	$-C_6H_5$	—n-Butyl

TABLE 13-continued



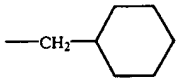
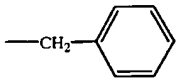
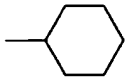
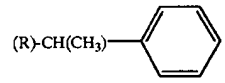
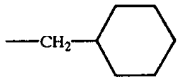
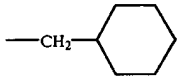
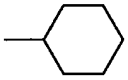
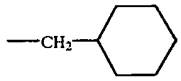
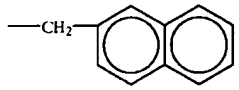
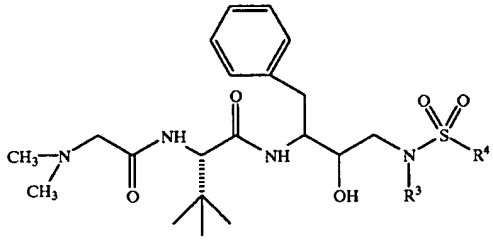
Entry	R^3	R^4
6		—n-Butyl
7		—n-Butyl
8		—n-Butyl
9	—i-Butyl	—n-Propyl
10	—i-Butyl	—$CH_2CH(CH_3)_2$
11		—n-Butyl
12		—i-Propyl
13		—$CH_2CH_2CH(CH_3)_2$
14	i-Butyl	—CH_2CH_3
15	i-Butyl	—$CH(CH_3)_2$
16	i-Butyl	
17		—$(CH_2)_2CH(CH_3)_2$
18	$(CH_2)_2CH(CH_3)_2$	—$CH(CH_3)_2$
19	i-Butyl	—$CH(CH_3)_2$
20	i-Butyl	—$C(CH_3)_3$
21		—$C(CH_3)_3$
22	—$(CH_2)_2CH(CH_3)_2$	—$C(CH_3)_3$
23	—$CH_2C_6H_5$	—$C(CH_3)_3$

TABLE 13-continued



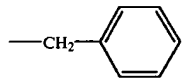
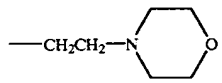
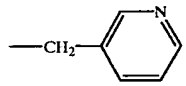
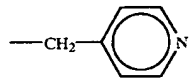
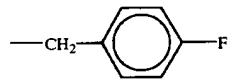
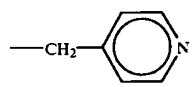
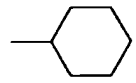
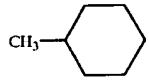
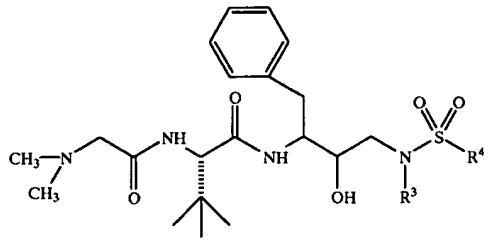
Entry	R^3	R^4
24	—$(CH_2)_2C_6H_5$	—$C(CH_3)_3$
25	n-Butyl	—$C(CH_3)_3$
26	n-Pentyl	—$C(CH_3)_3$
27	n-Hexyl	—$C(CH_3)_3$
28		—$C(CH_3)_3$
29	—$CH_2C(CH_3)_3$	—$C(CH_3)_3$
30		—$C(CH_3)_3$
31	—$CH_2C_6H_5OCH_3$(para)	—$C(CH_3)_3$
32		—$C(CH_3)_3$
33		—$C(CH_3)_3$
34	—$(CH_2)_2C(CH_3)_3$	—$C(CH_3)_3$
35	—$(CH_2)_4OH$	—$C(CH_3)_3$
36		—$C(CH_3)_3$
37		—$C(CH_3)_3$
38	—$CH_2CH(CH_3)_2$	—C_6H_5
39	i-amyl	—$CH_2C(CH_3)_3$
40		—$CH_2C(CH_3)_3$
41		—$CH_2C(CH_3)_3$
42	i-butyl	—$CH_2C(CH_3)_3$
43	—CH_2Ph	—Ph

TABLE 13-continued



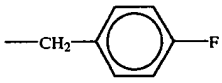
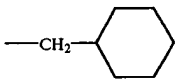
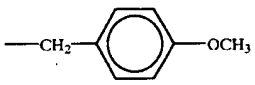
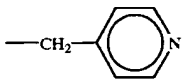
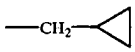
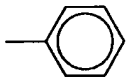
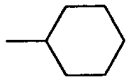
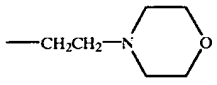
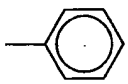
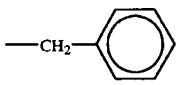
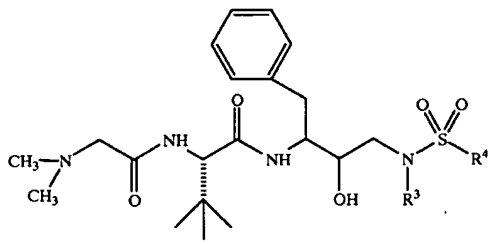
Entry	R^3	R^4
44		—Ph
45		—Ph
46		—Ph
47		—Ph
48		—Ph
49	$-CH_2CH=CH_2$	—Ph
50		—Ph
51		—Ph
52	$-CH_2CH_2Ph$	—Ph
53	$-CH_2CH_2CH_2CH_2OH$	—Ph
54	$-CH_2CH_2N(CH_3)_2$	—Ph
55		—Ph
56	$-CH_3$	—Ph
57	$-CH_2CH_2CH_2SCH_3$	—Ph
58	$-CH_2CH_2CH_2S(O)_2CH_3$	—Ph
59	$-CH_2CH_2CH(CH_3)_2$	
60	$-CH_2CH_2CH(CH_3)_2$	

TABLE 13-continued



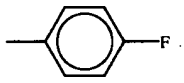
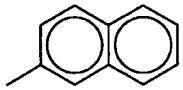
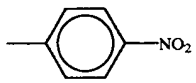
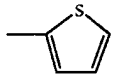
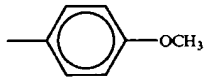
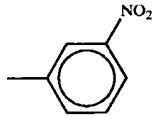
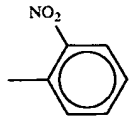
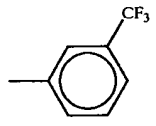
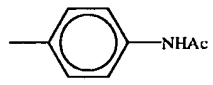
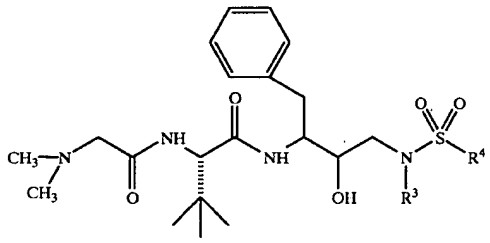
Entry	R^3	R^4
61	$-CH_2CH_2CH(CH_3)_2$	$-CH_2CH_2CH_3$
62	$-CH_2CH_2CH(CH_3)_2$	$-CH_3$
63	$-CH_2CH_2CH(CH_3)_2$	
64	$-CH_2CH_2CH(CH_3)_2$	
65	$-CH_2CH_2CH(CH_3)_2$	
66	$-CH_2CH_2CH(CH_3)_2$	
67	$-CH_2CH_2CH(CH_3)_2$	
68	$-CH_2CH_2CH(CH_3)_2$	
69	$-CH_2CH_2CH(CH_3)_2$	
70	$-CH_2CH_2CH(CH_3)_2$	
71	$-CH_2CH_2CH(CH_3)_2$	

TABLE 13-continued



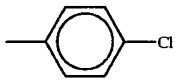
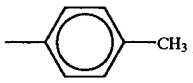
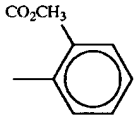
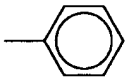
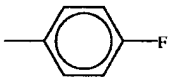
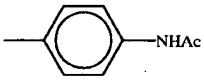
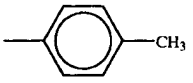
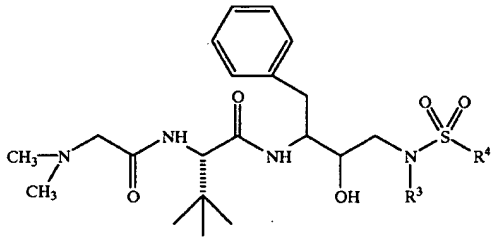
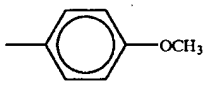
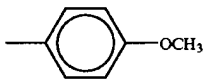
Entry	R^3	R^4
72	$-CH_2CH_2CH(CH_3)_2$	
73	$-CH_2CH_2CH(CH_3)_2$	
74	$-CH_2CH_2CH(CH_3)_2$	
75	$-CH_2CH(CH_3)_2$	
76	$-CH_2CH(CH_3)_2$	
77	$-CH_2CH(CH_3)_2$	
78	$-CH_2CH(CH_3)_2$	

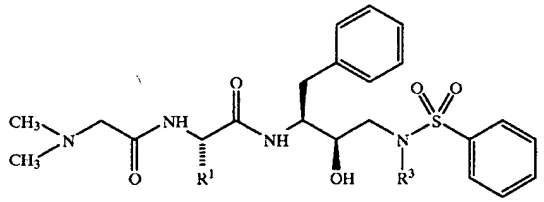
TABLE 13-continued



Entry	R^3	R^4
79	$-CH_2CH_2CH_3$	
80	$-CH_2CH_2CH_2CH_3$	

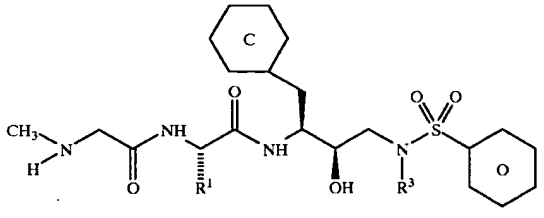
[a]benzyloxycarbonyl
[b]2-quinolinylcarbonyl

TABLE 14



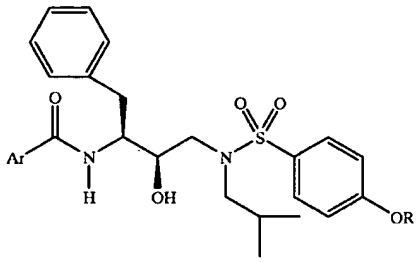
Entry	R^1	R^3
1	$C(CH_3)_3$	$CH_2CH_2CH(CH_3)_2$
2	$CH_2C{\equiv}CH$	$CH_2CH_2CH(CH_3)_2$
3	$C(CH_3)_2(SCH_3)$	$CH_2CH_2CH(CH_3)_2$
4	$C(CH_3)_2(S[O]CH_3)$	$CH_2CH_2CH(CH_3)_2$
5	$C(CH_3)_2(S[O]_2CH_3)$	$CH_2CH_2CH(CH_3)_2$
6	$C(CH_3)_3$	$CH_2CH(CH_3)_2$
7	$C(CH_3)_3$	cyclohexyl
8	$CH(CH_3)_2$	$CH_2CH(CH_3)_2$
9	$CH(CH_2CH_3)(CH_3)$	$CH_2CH(CH_3)_2$

TABLE 14A



Entry	R^1	R^3
1	$C(CH_3)SCH_3$	$CH_2CH_2CH(CH_3)_2$

TABLE 15



R = CH_3, H

Ar

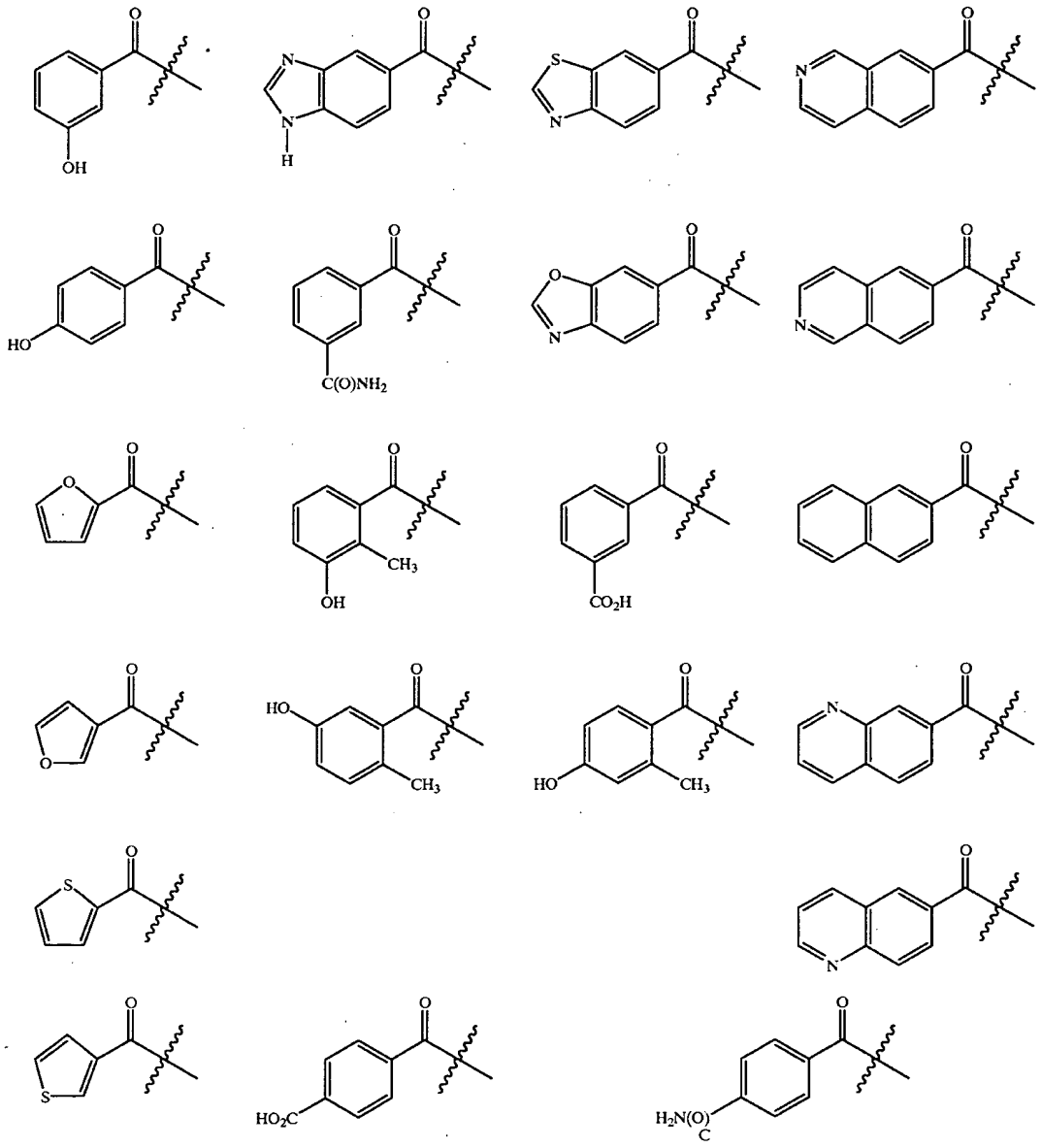
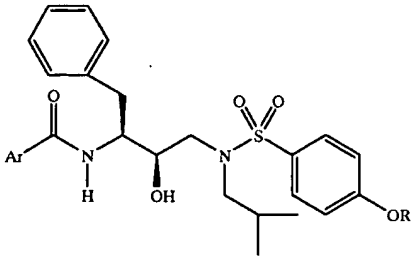


TABLE 15-continued



R = CH_3, H

Ar

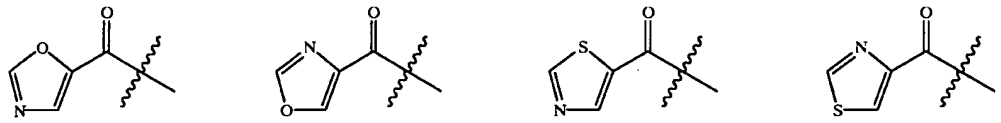
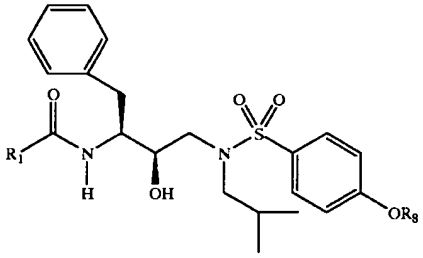


TABLE 16



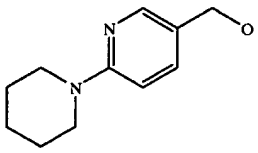
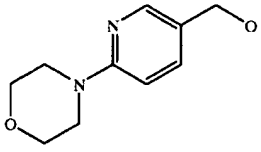
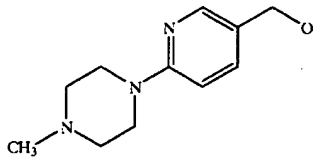
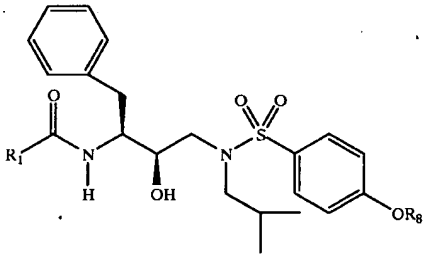
R_1	R_8
	H or CH_3
	H or CH_3
	H or CH_3

TABLE 16-continued



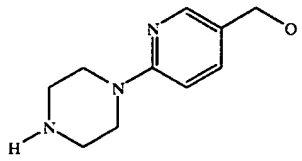
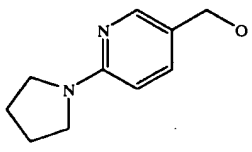
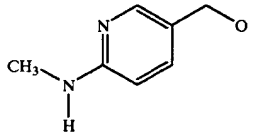
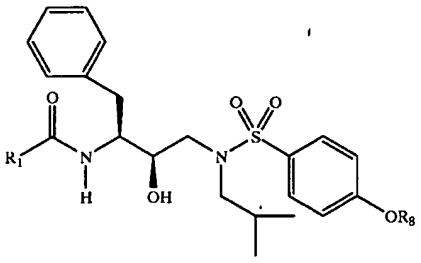
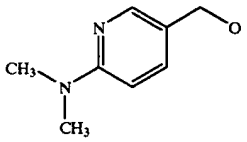
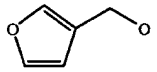
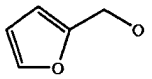
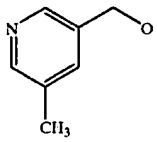
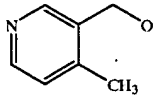
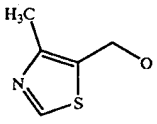
R_1	R_8
	H or CH_3
	H or CH_3
	H or CH_3

TABLE 16-continued



R_1	R_8
	H or CH_3
	H or CH_3
	H or CH_3
	H or CH_3
	H or CH_3
	H or CH_3

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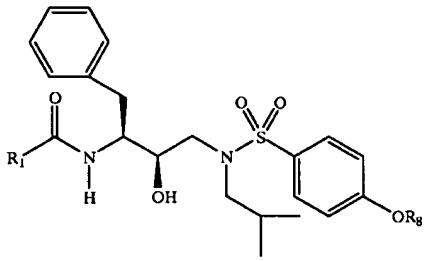


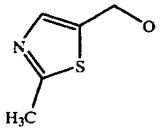
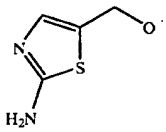
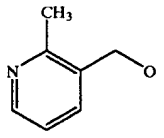
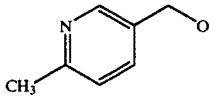
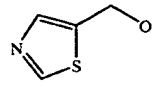
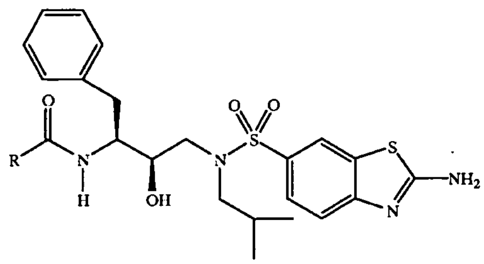
R_1	R_8
	H or CH_3
	H or CH_3
	H or CH_3
	H or CH_3
	H or CH_3

TABLE 16A



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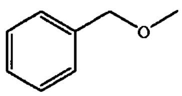
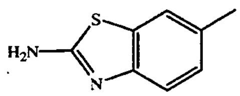
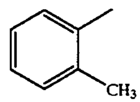
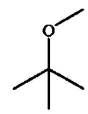
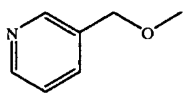
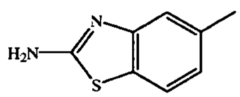
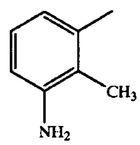
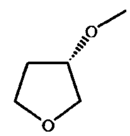
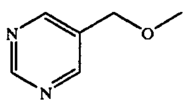
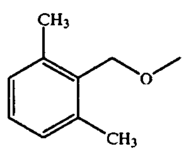
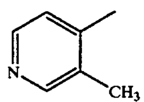
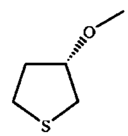
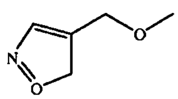
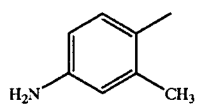
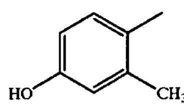
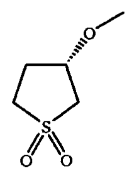
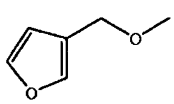
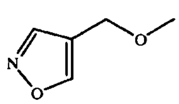
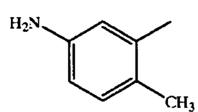
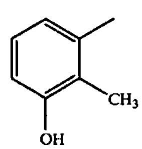
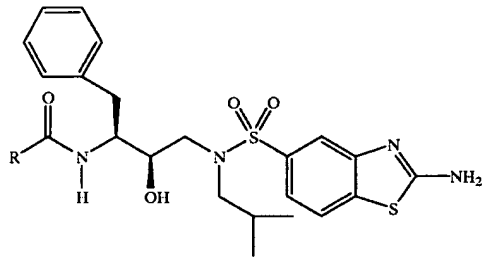
			
			
			
			
			
			

TABLE 16B



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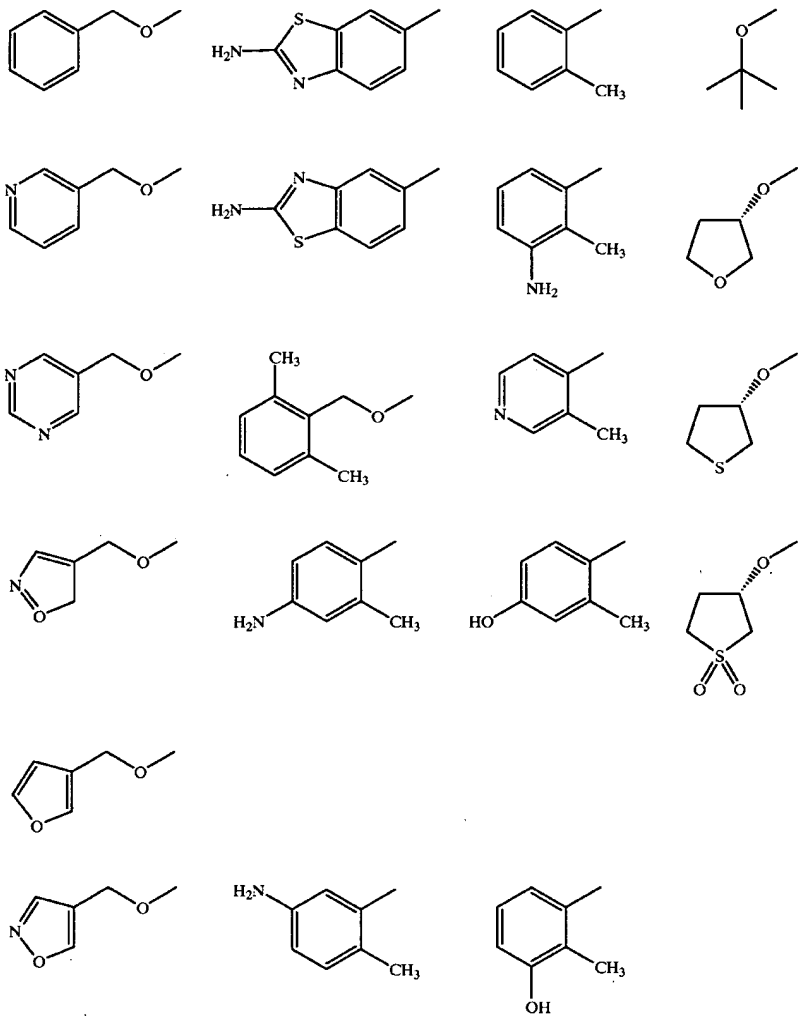
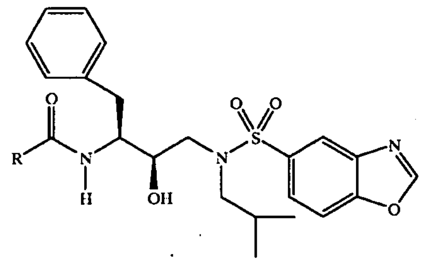


TABLE 16C



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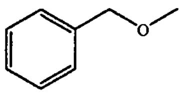	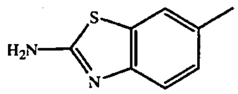	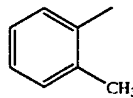	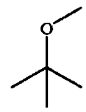
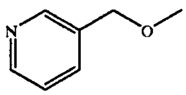	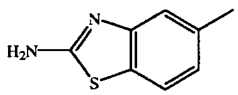	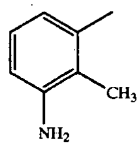	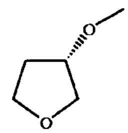
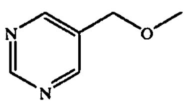	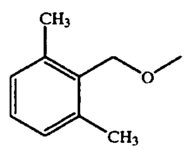	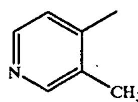	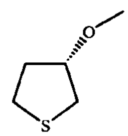
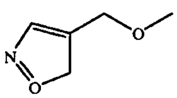	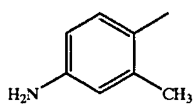	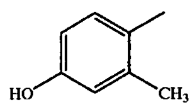	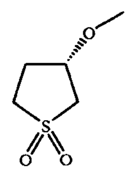
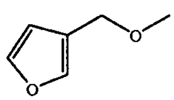			
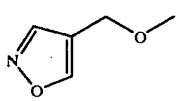	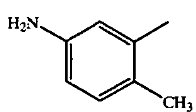	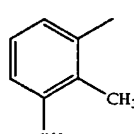	

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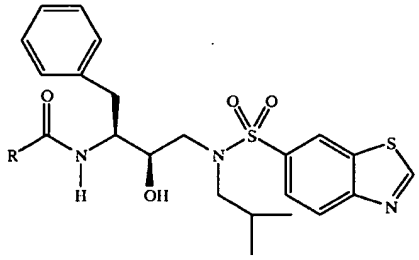

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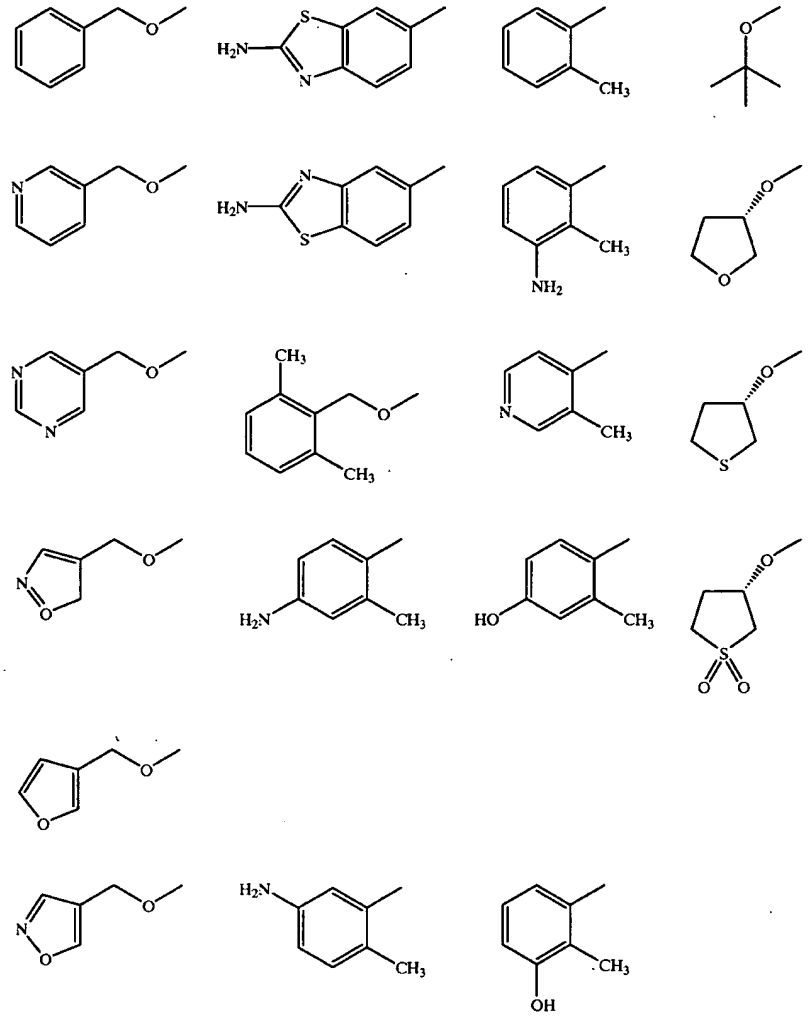
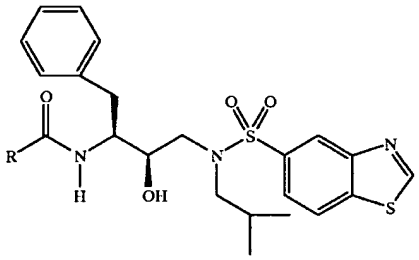


TABLE 16E



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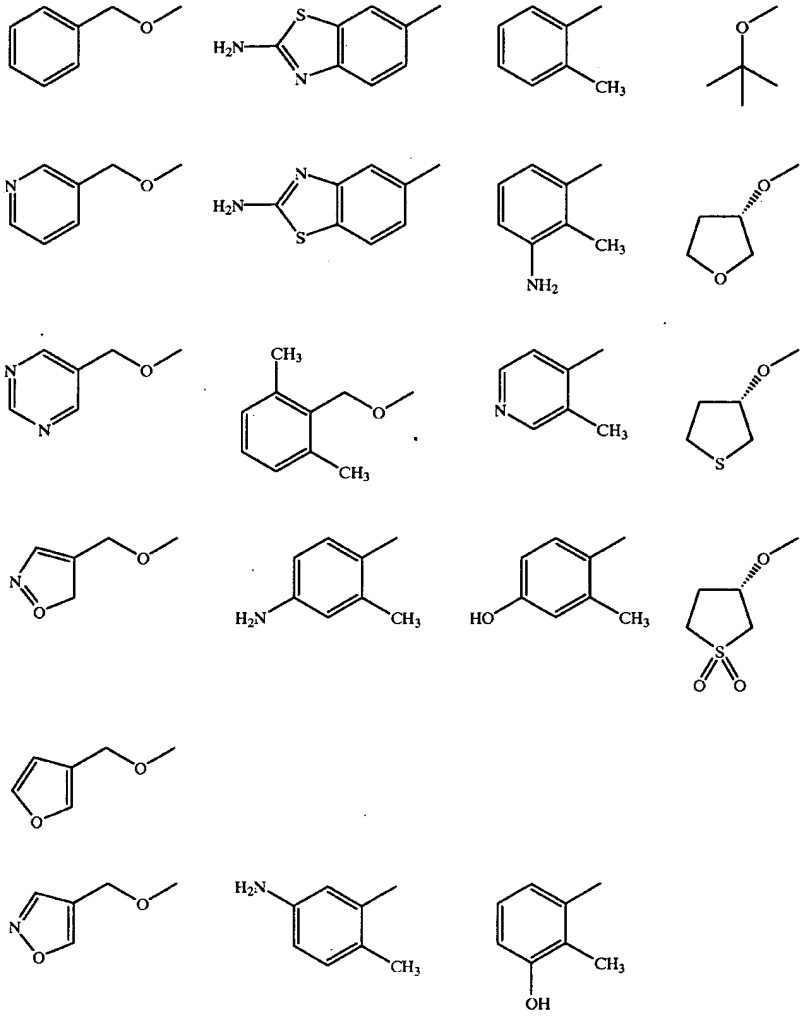
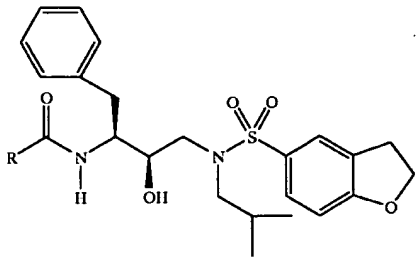


TABLE 16F



R

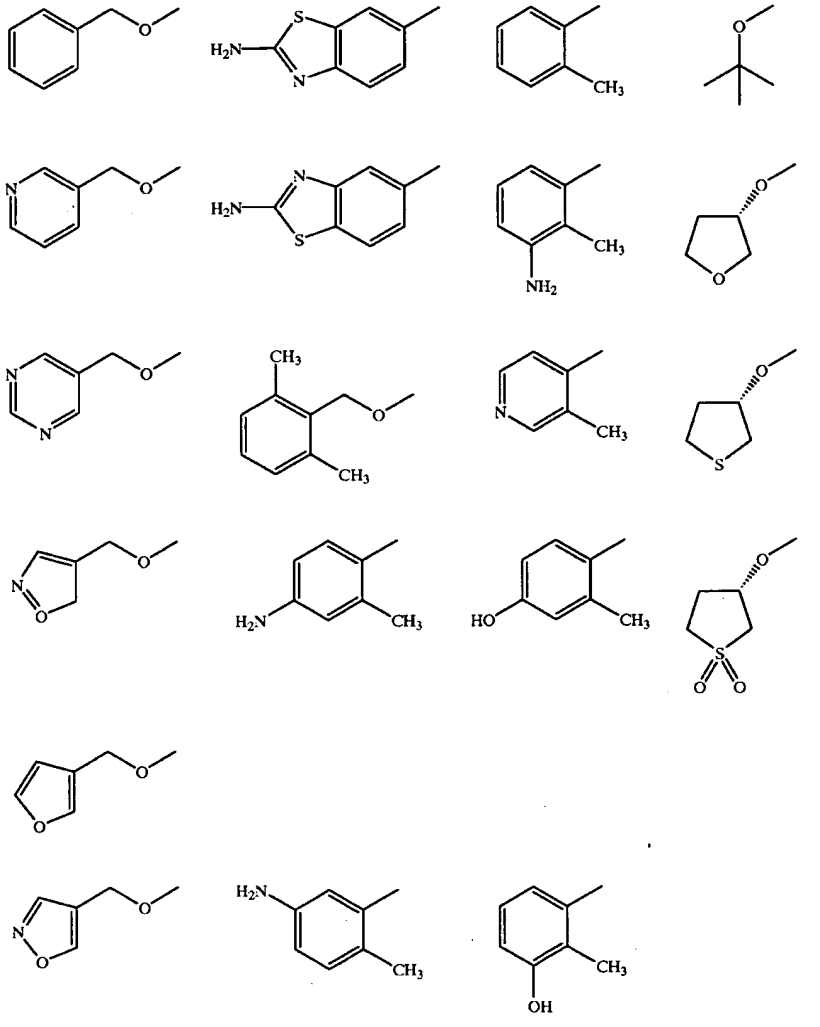
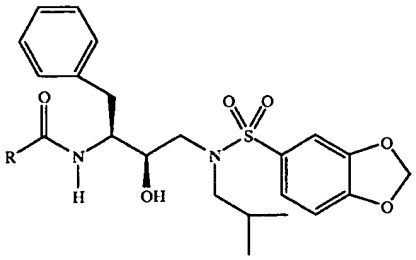


TABLE 16G



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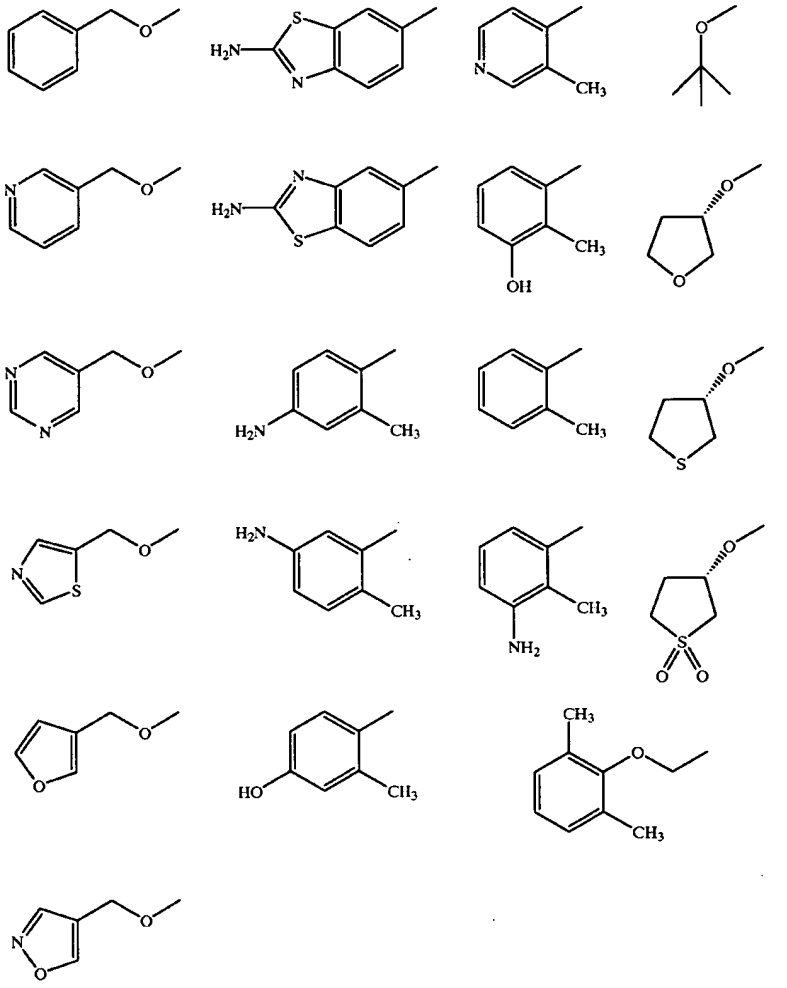
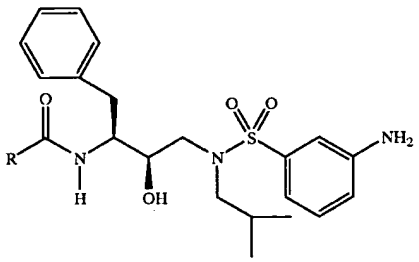


TABLE 16H



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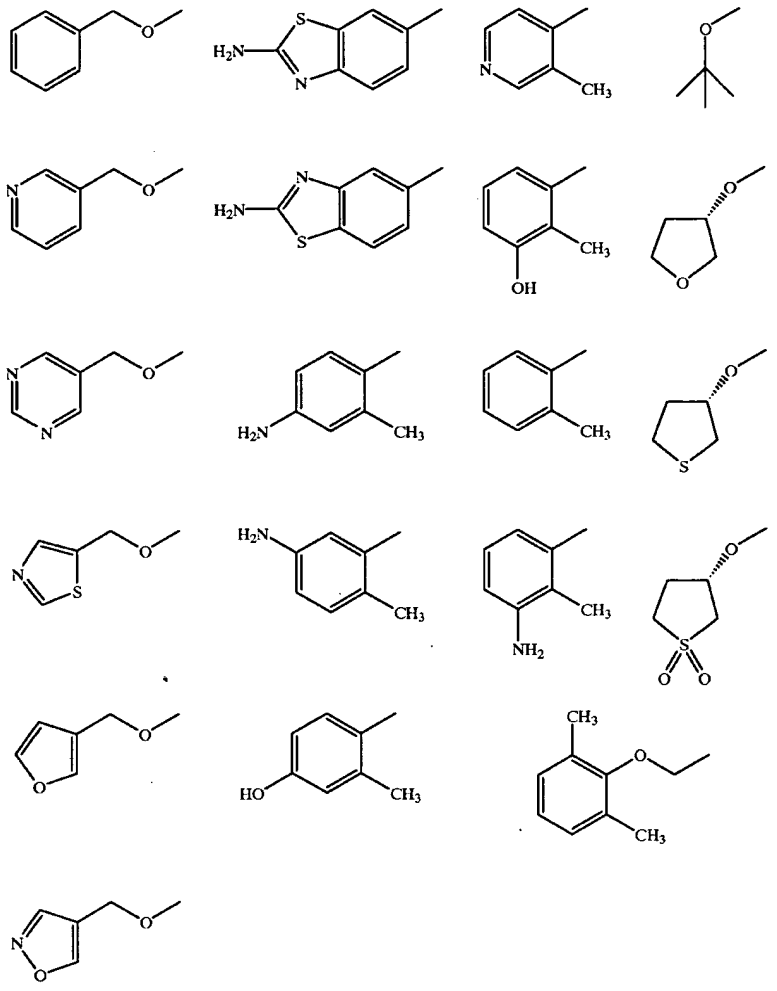
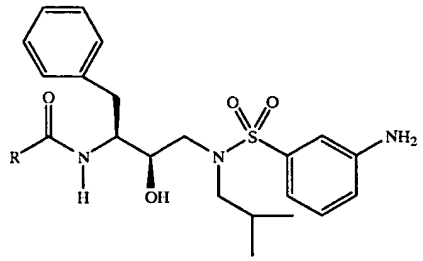


TABLE 16I



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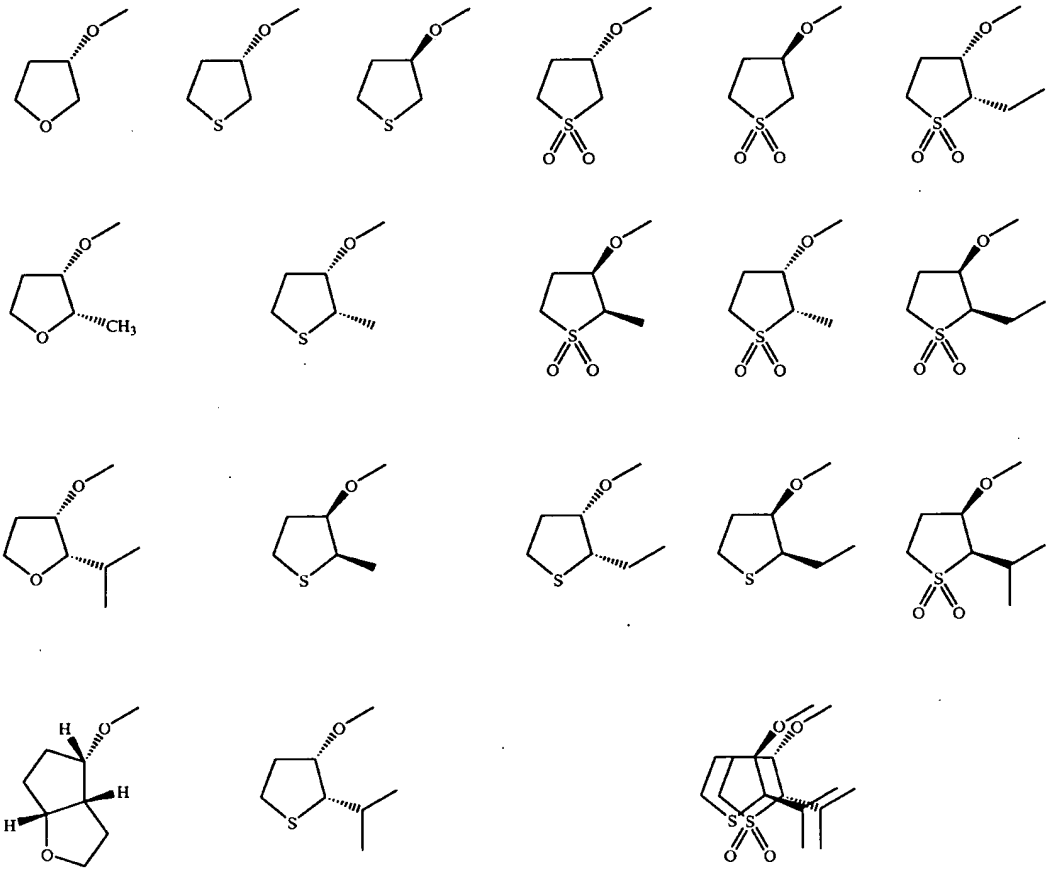

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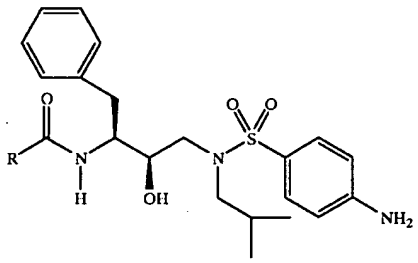

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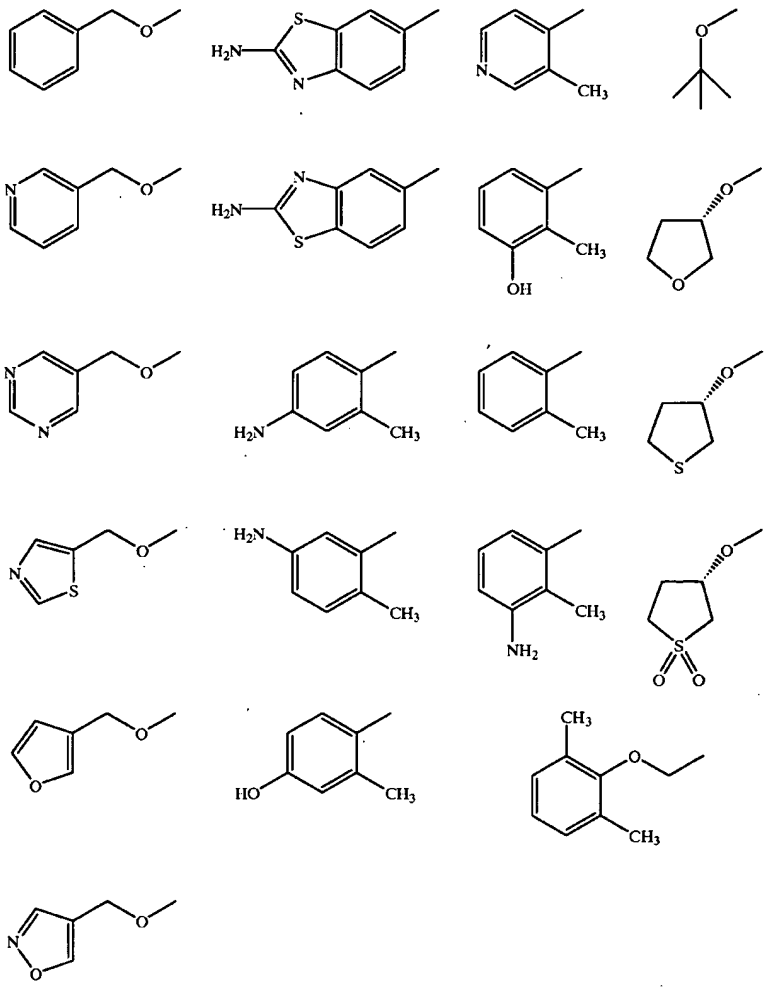

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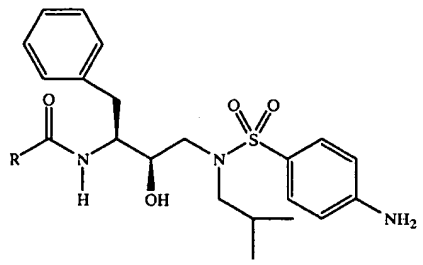

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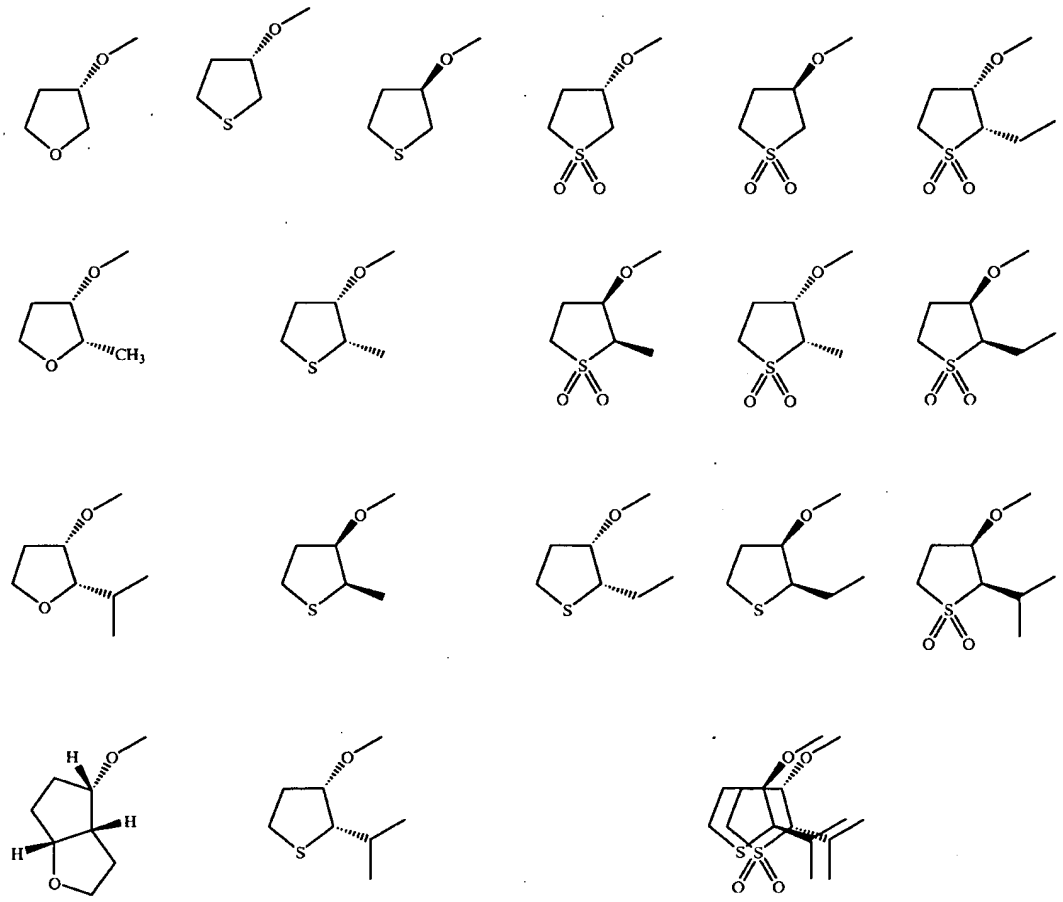

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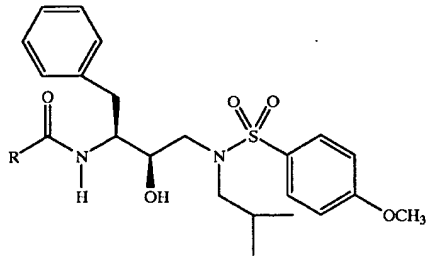

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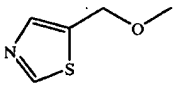

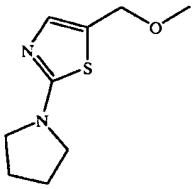

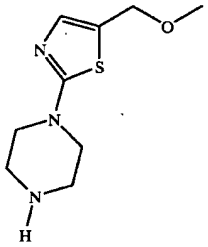

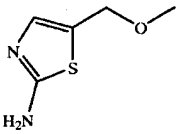

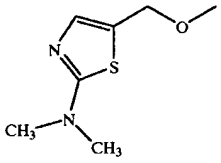

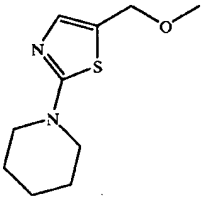

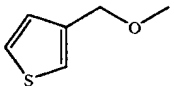

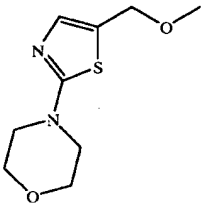

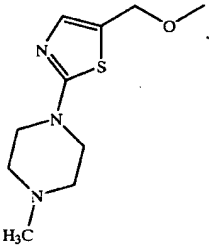

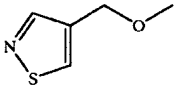

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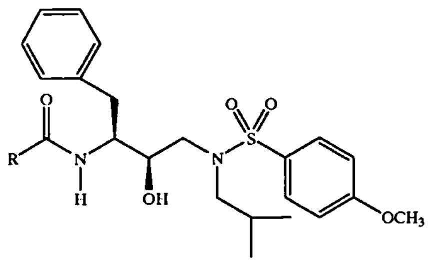

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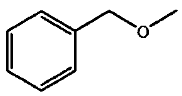
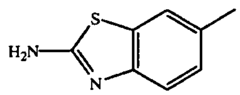
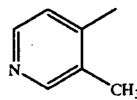
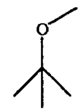
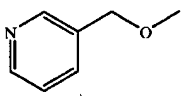
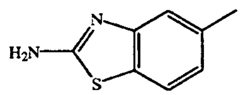
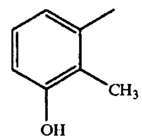
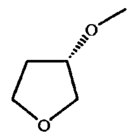
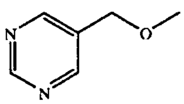
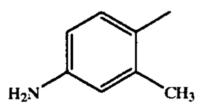
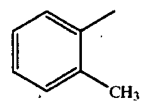
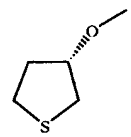
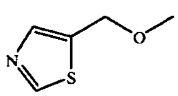
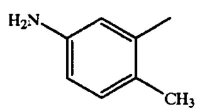
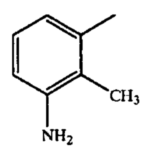
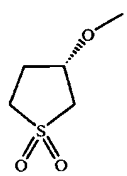
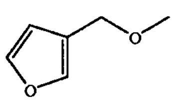
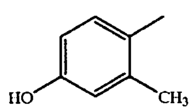
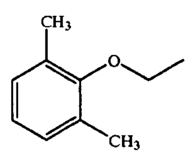
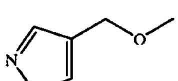
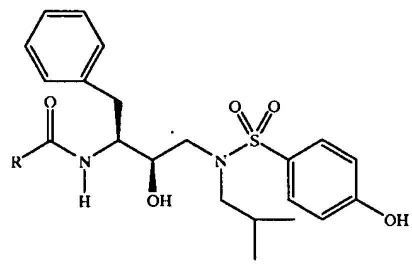
			
			
			
			
			
			

TABLE 16N



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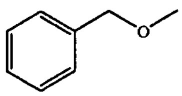
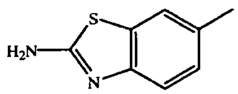
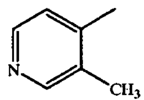
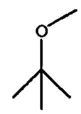
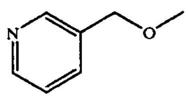
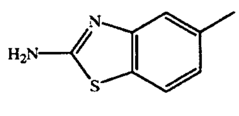
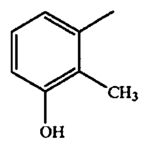
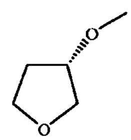
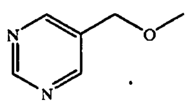
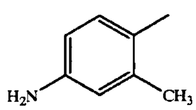
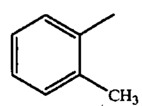
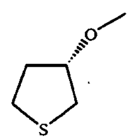
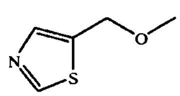
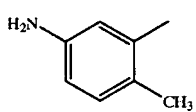
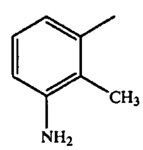
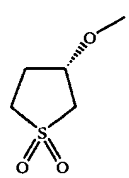
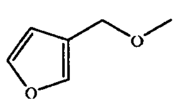
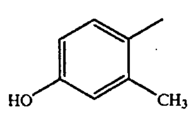
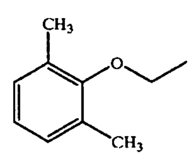





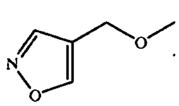
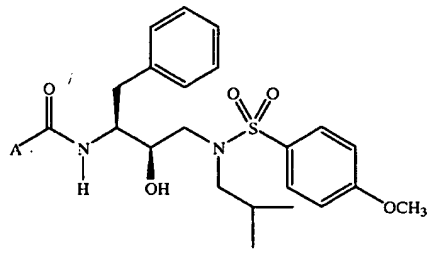


TABLE 17



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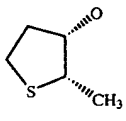
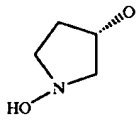
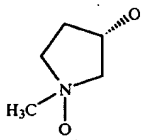
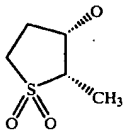
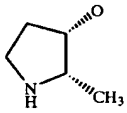
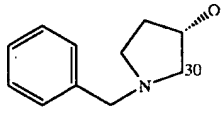

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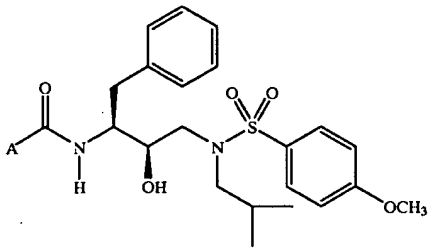


A

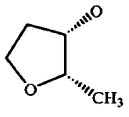
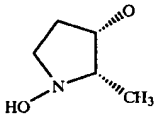
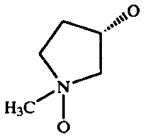
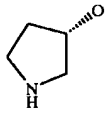
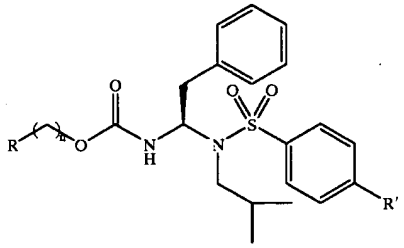





TABLE 17A



R

n = 0, 1 or 2
R' = —OH, —OCH_3, —OBz,
—$C(NH_2)$ = NOH or —$C(NH_2)$ = NH

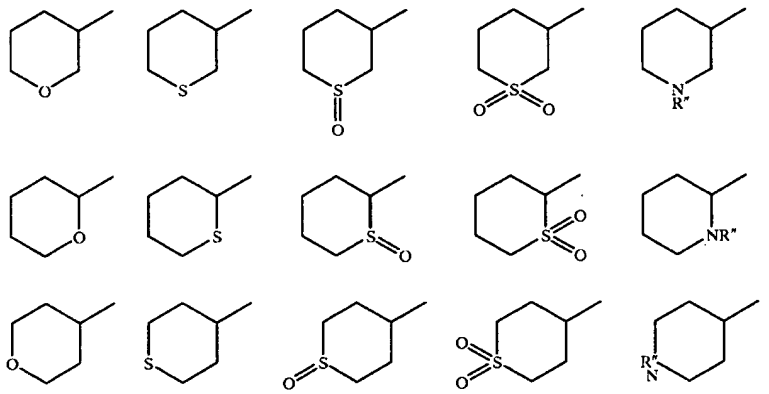
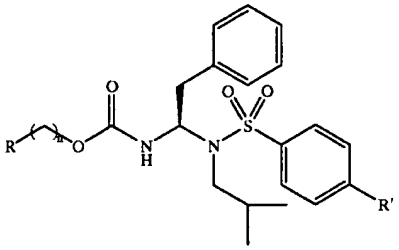


TABLE 17A-continued



R

n = 0, 1 or 2
R' = —OH, —OCH_3, —OBz,
—$C(NH_2)$ = NOH or —$C(NH_2)$ = NH

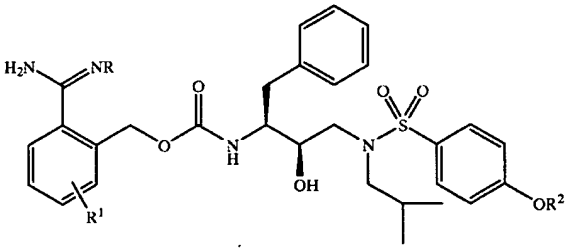
R" = —H or lower alkyl

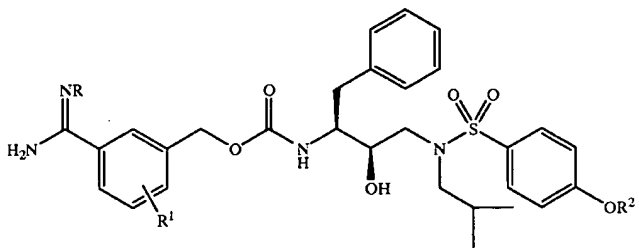
TABLE 17B

R = H or OH

R^1 = CH_3, NH_2, F, Cl or Br

R^2 = H or CH_3





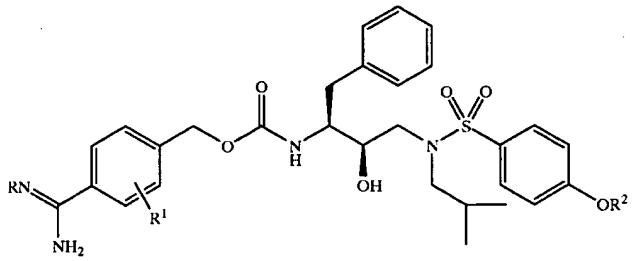
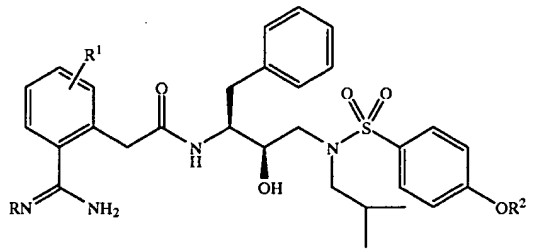
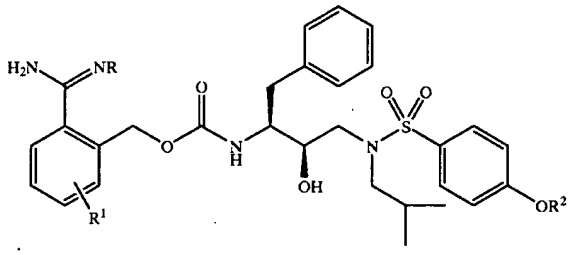
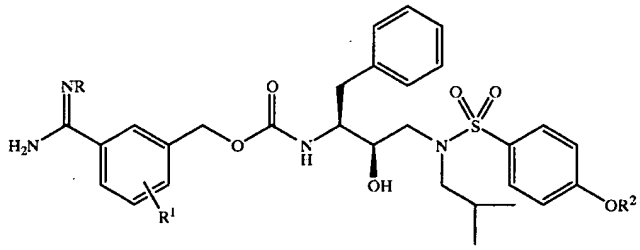
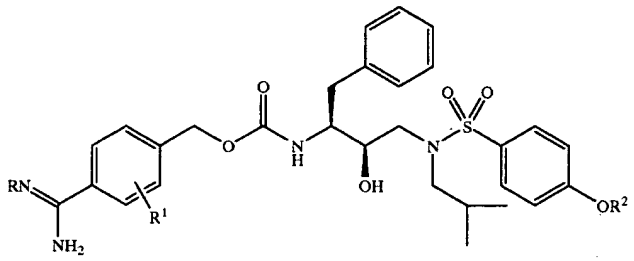


TABLE 17B-continued









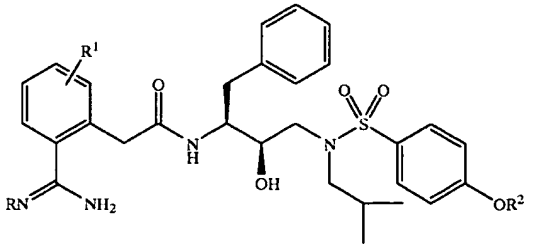
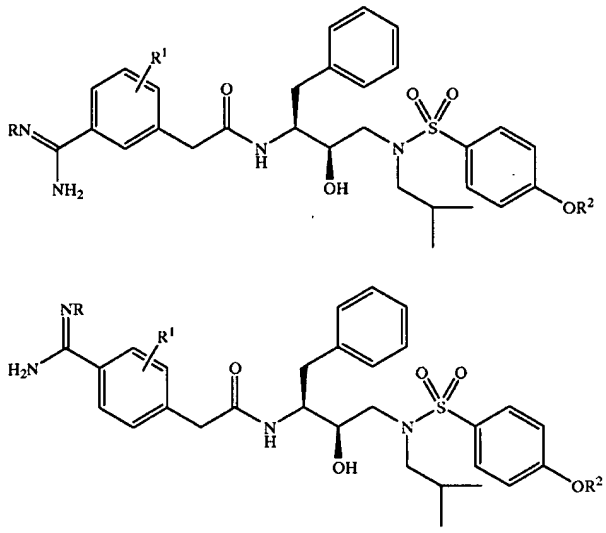


TABLE 17B-continued



EXAMPLE 23

The compounds of the present invention are effective HIV protease inhibitors. Utilizing an enzyme assay as described below, the compounds set forth in the examples herein disclosed inhibited the HIV enzyme. The preferred compounds of the present invention and their calculated IC_{50} (inhibiting concentration 50%, i.e., the concentration at which the inhibitor compound reduces enzyme activity by 50%) values are shown in Tables 18 through 21. The enzyme method is described below. The substrate is 2-Ile-Nle-Phe (p-NO_2)-Gln-ArgNH_2. The positive control is MVT-101 (Miller, M. et al, *Science,* 246, 1149 (1989)] The assay conditions are as follows:

Assay buffer:

20 mM sodium phosphate, pH 6.4

20% glycerol

1 mM EDTA

1 mM DTT

0.1% CHAPS

The above described substrate is dissolved in DMSO, then diluted 10 fold in assay buffer. Final substrate concentration in the assay is 80 μM.

HIV protease is diluted in the assay buffer to a final enzyme concentration of 12.3 nanomolar, based on a molecular weight of 10,780.

The final concentration of DMSO is 14% and the final concentration of glycerol is 18%. The test compound is dissolved in DMSO and diluted in DMSO to 10× the test concentration; 10 μl of the enzyme preparation is added, the materials mixed and then the mixture is incubated at ambient temperature for 15 minutes. The enzyme reaction is initiated by the addition of 40 μl of substrate. The increase in fluorescence is monitored at 4 time points (0, 8, 16 and 24 minutes) at ambient temperature. Each assay is carried out in duplicate wells.

The preceding examples can be repeated with similar success by substituting the generically or specifically described reactants and/or operating conditions of this invention for those used in the preceding examples.

TABLE 18A

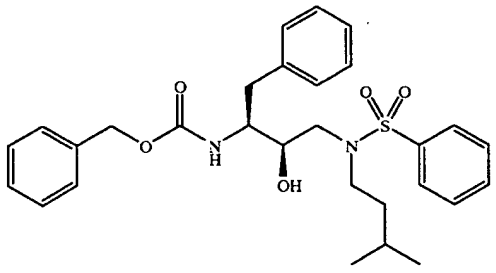
Entry	Compound	IC_{50} (nanomolar)
1		16

TABLE 18A-continued

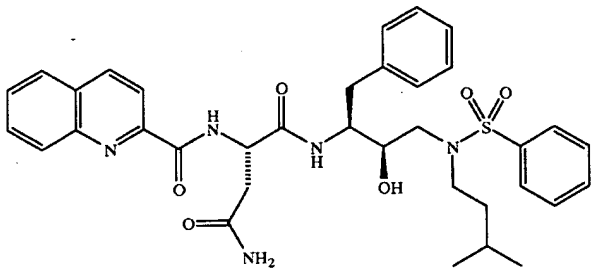
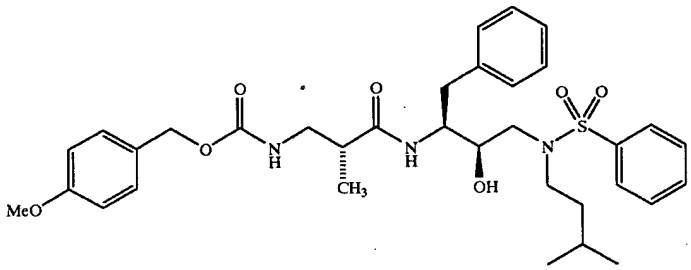
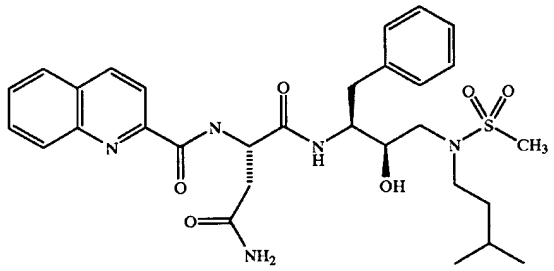
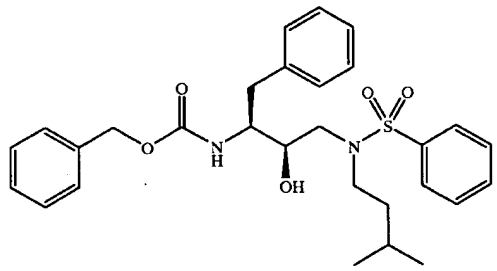
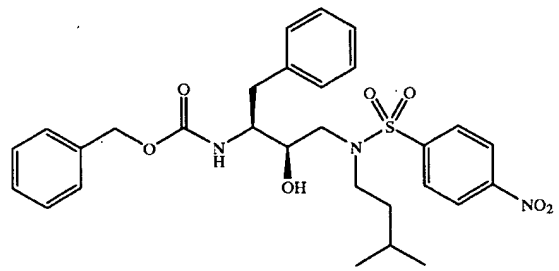
Entry	Compound	IC_{50} (nanomolar)
2		1.5
3		1.4
4		27
5		19
6		10

TABLE 18A-continued

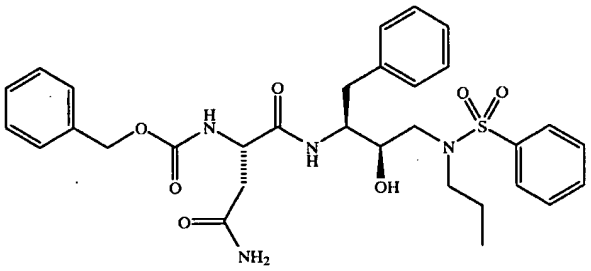
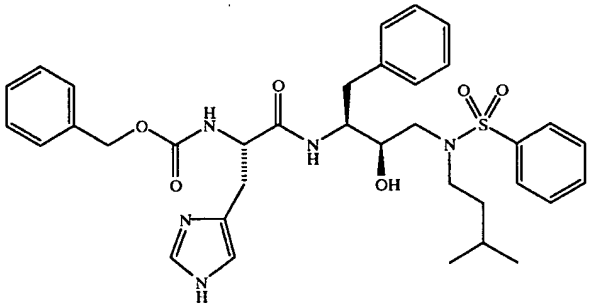
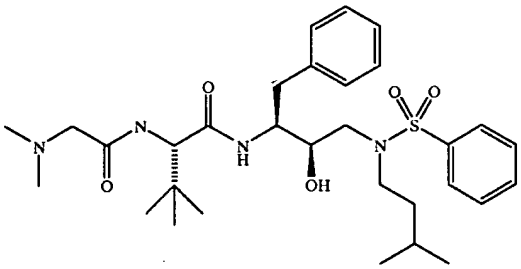
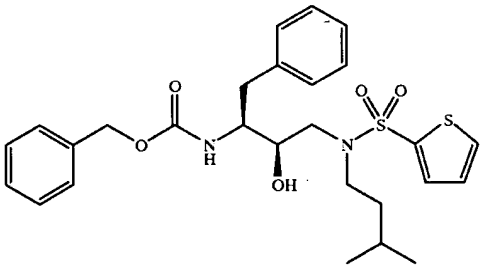
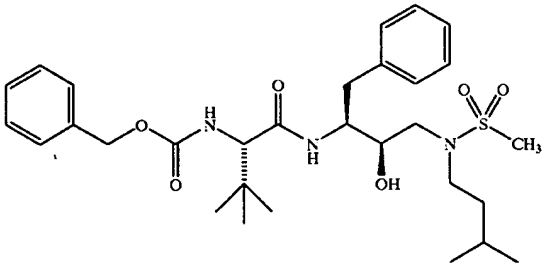
Entry	Compound	IC_{50} (nanomolar)
7		3.6
8		4.2
9		3.5
10		100
11		81

TABLE 18A-continued

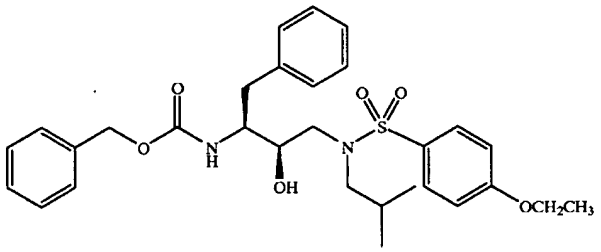
Entry	Compound	IC_{50} (nanomolar)
12		20

TABLE 19B

Ex.	Table	Entry	IC_{50} (uM) or % inhib
6	1a	1	0.011
6	1a	2	0.010
6	1a	3	38% @ 1 uM, 79% @ 10 uM
6	1a	4	0.016
6	1a	5	0.10
6	1a	6	36% @ 10 uM
6	1a	7	0.0096
6	1a	39	0.016
6	1a	40	0.21
6	1a	41	24% @ 1 uM, 74% @ 10 uM
6	1a	50	42% @ 1 uM, 89% @ 10 uM
6	1a	51	31% @ 1 uM, 76% @ 10 uM
6	1a	52	39% @ 1 uM, 81% @ 10 uM
6	1a	53	0.049
6	1a	54	0.0028
6	1a	55	0.10
6	1a	56	0.0036
16	3	1	0.081
16	3	2	38% @ 0.1 uM, 90% @ 1.0 uM
16	3	4	0.0024
16	3	6	0.0018
16	3	8	0.003
16	3	10	0.0025
16	3	12	0.0016
16	4	102	0.0015
16	5	1	0.0014
16	5	14	0.0022
16	5	22	0.0018
16	5	33	0.0044
16	5	34	0.0020
16	7	31	0.0028
16	7	32	0.0015
16	11	1	0.13
16	11	9	41% @ 0.1 uM, 86% @ 1 uM
16	12	10	0.0033
16	14	3	0.0049
16	14	10	0.0032

TABLE 20

Table	Entry	IC_{50} (uM) or % inhibtion
1A	3	0.02
5A	1	0.04
5A	3	0.02
5A	4	0.01
5A	5	0.026
5A	6	0.023
5A	7	0.007
5A	9	0.067
5A	11	0.018
5A	12	0.006
5A	13	0.0098

TABLE 20-continued

Table	Entry	IC_{50} (uM) or % inhibtion
5A	14	0.049
5A	16	0.008
5A	17	59% @ 10 μM
5A	18	0.13
5A	19	0.092
5A	20	85% @ 1 μM
5A	22	63% @ 1 μM
5A	24	0.047
5A	25	0.014
5A	26	0.005
5A	28	0.015
5A	29	0.19
5A	30	0.03
5A	31	0.02

EXAMPLE 24

The effectiveness of various compounds were determined in the above-described enzyme assay and in a CEM cell assay.

The HIV inhibition assay method of acutely infected cells is an automated tetrazolium based colorimetric assay essentially that reported by Pauwles et al, *J. Virol. Methods,* 20, 309–321 (1988). Assays were performed in 96-well tissue culture plates. CEM cells, a $CD4^+$ cell line, were grown in RPMI-1640 medium (Gibco) supplemented with a 10% fetal calf serum and were then treated with polybrene (2 μg/ml). An 80 μl volume of medium containing 1×10^4 cells was dispensed into each well of the tissue culture plate. To each well was added a 100 μl volume of test compound dissolved in tissue culture medium (or medium without test compound as a control) to achieve the desired final concentration and the cells were incubated at 37° C. for 1 hour. A frozen culture of HIV-1 was diluted in culture medium to a concentration of 5×10^4 $TCID_{50}$ per ml ($TCID_{50}$=the dose of virus that infects 50% of cells in tissue culture), and a 20 μL volume of the virus sample (containing 1000 $TCID_{50}$ of virus) was added to wells containing test compound and to wells containing only medium (infected control cells). Several wells received culture medium without virus (uninfected control cells). Likewise, the intrinsic toxicity of the test compound was determined by adding medium without virus

to several wells containing test compound. In summary, the tissue culture plates contained the following experiments:

	Cells	Drug	Virus
1.	+	-	-
2.	+	+	-
3.	+	-	+
4.	+	+	+

In experiments 2 and 4 the final concentrations of test compounds were 1, 10, 100 and 500 μg/ml. Either azidothymidine (AZT) or dideoxyinosine (ddI) was included as a positive drug control. Test compounds were dissolved in DMSO and diluted into tissue culture medium so that the final DMSO concentration did not exceed 1.5% in any case. DMSO was added to all control wells at an appropriate concentration.

Following the addition of virus, cells were incubated at 37° C. in a humidified, 5% CO_2 atmosphere for 7 days. Test compounds could be added on days 0, 2 and 5 if desired. On day 7, post-infection, the cells in each well were resuspended and a 100 μl sample of each cell suspension was removed for assay. A 20 μL volume of a 5 mg/ml solution of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) was added to each 100 μL cell suspension, and the cells were incubated for 4 hours at 27° C. in a 5% CO_2 environment. During this incubation, MTT is metabolically reduced by living cells resulting in the production in the cell of a colored formazan product. To each sample was added 100 μl of 10% sodium dodecylsulfate in 0.01 N HCl to lyse the cells, and samples were incubated overnight. The absorbance at 590 nm was determined for each sample using a Molecular Devices microplate reader. Absorbance values for each set of wells is compared to assess viral control infection, uninfected control cell response as well as test compound by cytotoxicity and antiviral efficacy.

TABLE 21

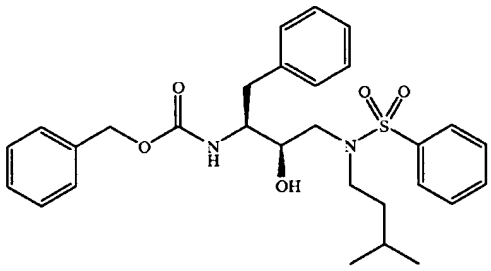
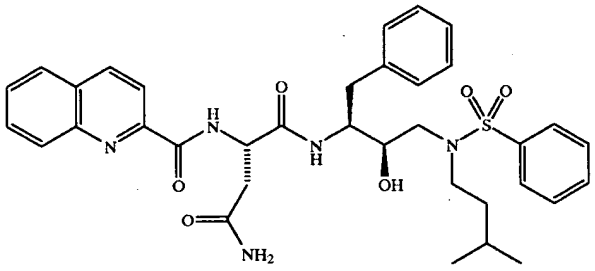
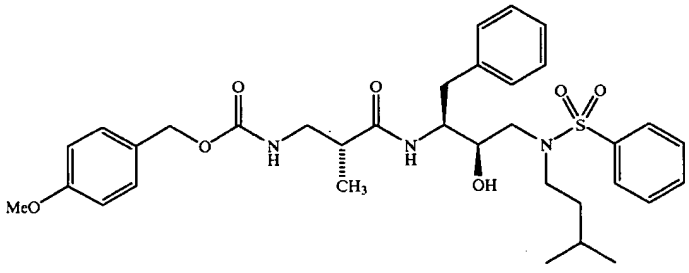
Entry	Compound	IC_{50} (nM)	EC_{50} (nM)	TD_{50} (nM)
1		16	55	27
2		1	5	203
3		1	11	780

TABLE 21-continued

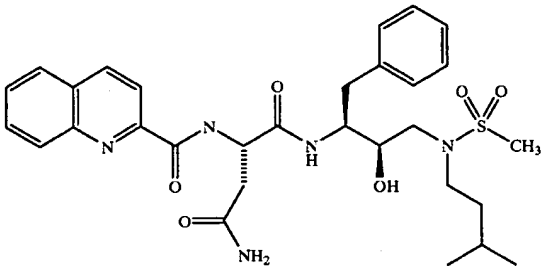
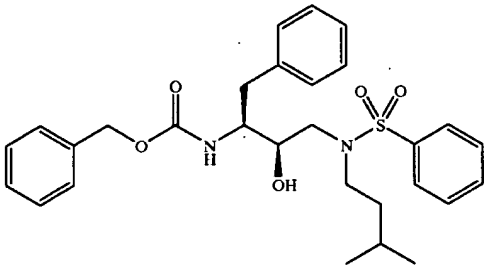
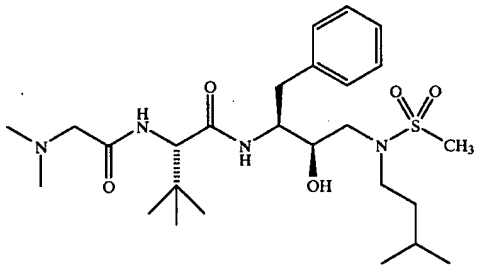
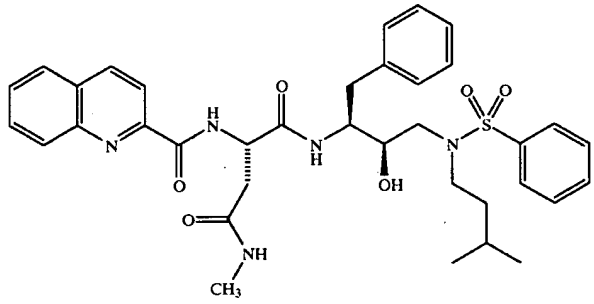
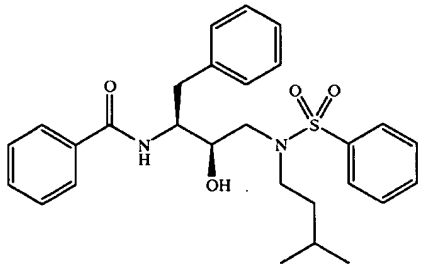
Entry	Compound	IC_{50} (nM)	EC_{50} (nM)	TD_{50} (nM)
4		27	64	28
5		19	88	11
6		>100	380	425
7		3	25	39
8		85	1200	24

TABLE 21-continued

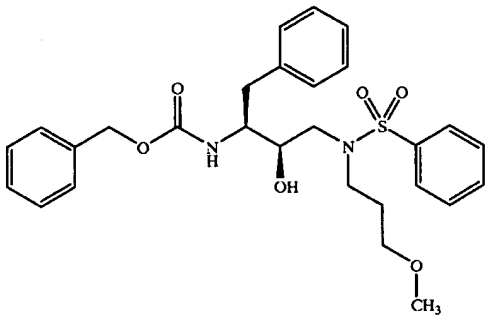
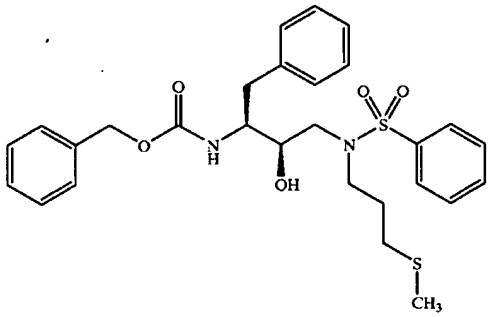
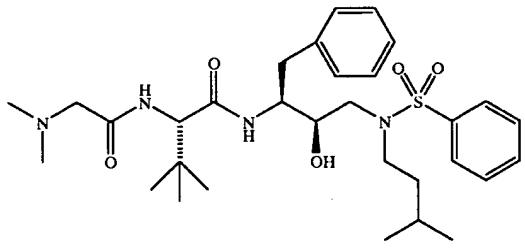
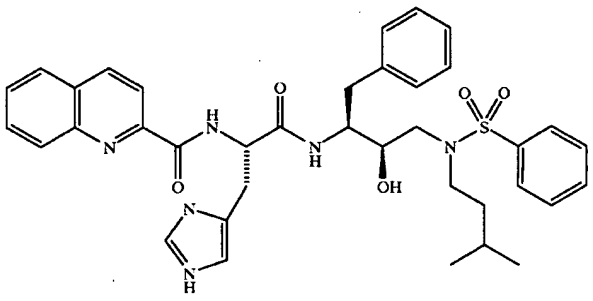
Entry	Compound	IC_{50} (nM)	EC_{50} (nM)	TD_{50} (nM)
9		53	398	15
10		45	700	12
11		3	11	54
12		2	12	7.5

TABLE 21-continued

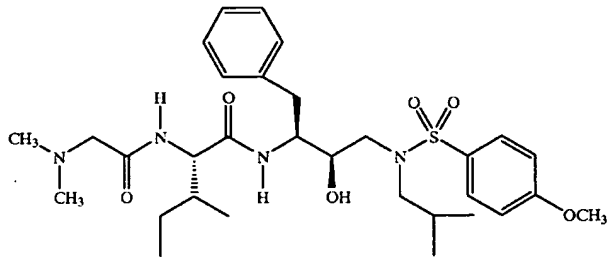
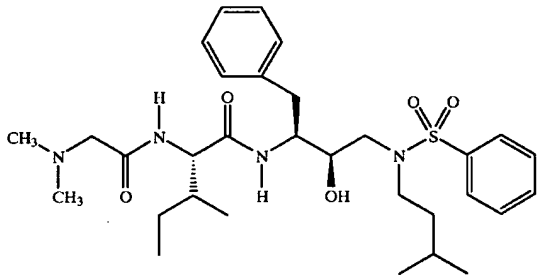
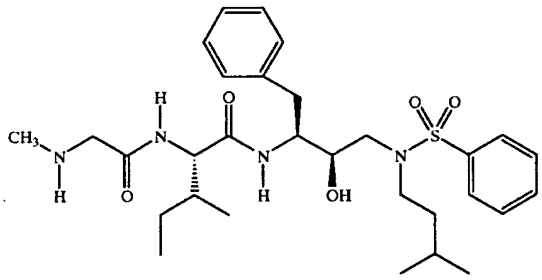
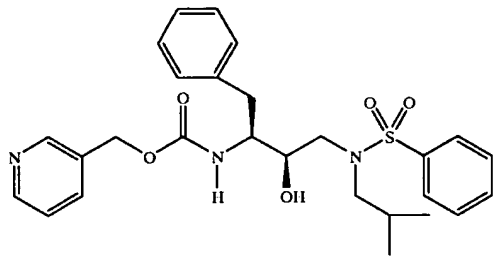
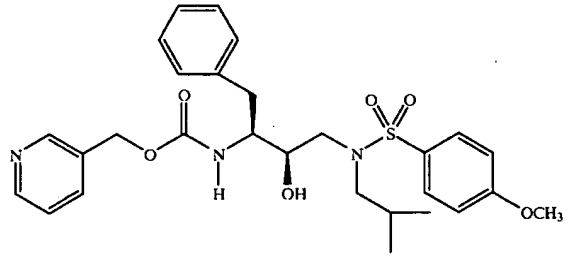
Entry	Compound	IC_{50} (nM)	EC_{50} (nM)	TD_{50} (nM)
13		3	<16	
14		4	15	55,000
15		5	38	
16		9	80	62,000
17		4	5	59,000

TABLE 21-continued

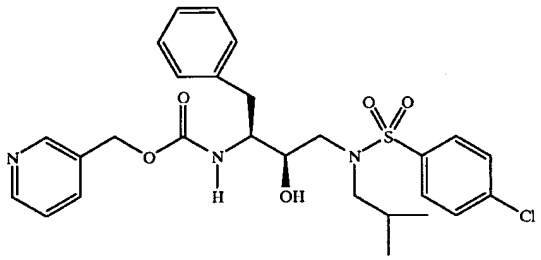
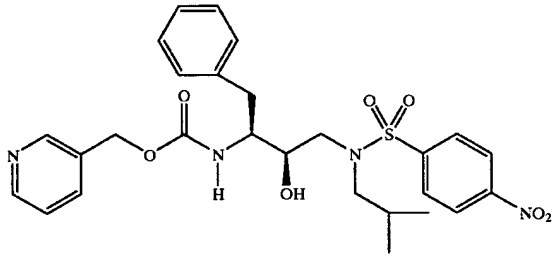
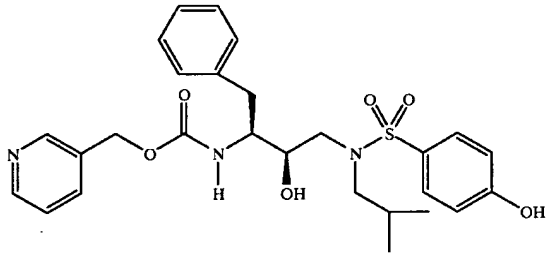
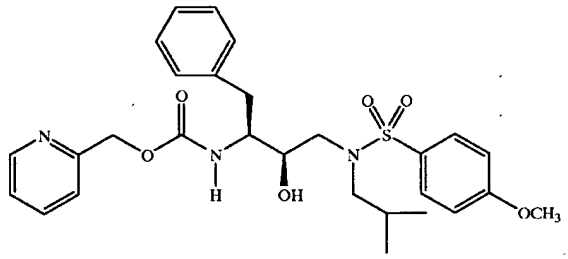
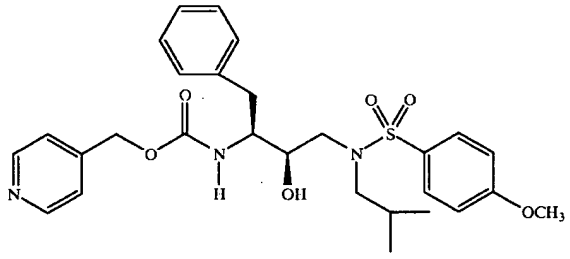
Entry	Compound	IC_{50} (nM)	EC_{50} (nM)	TD_{50} (nM)
18		4	154	
19		8	377	
20		4	13	
21		73		
22		15	18	31,000

TABLE 21-continued

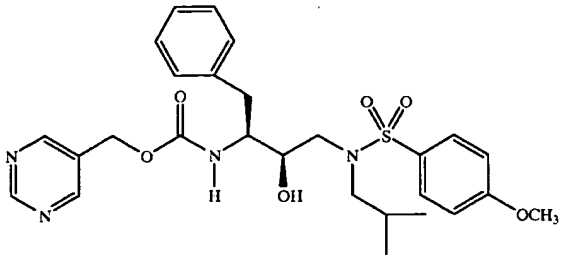
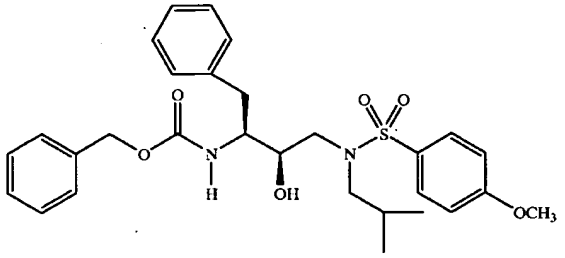
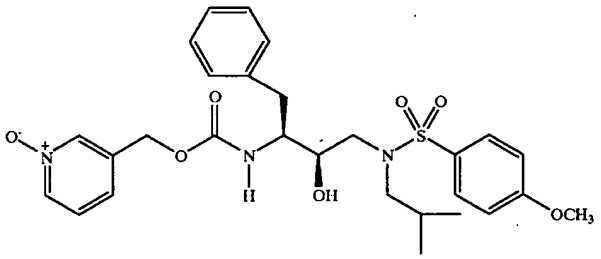
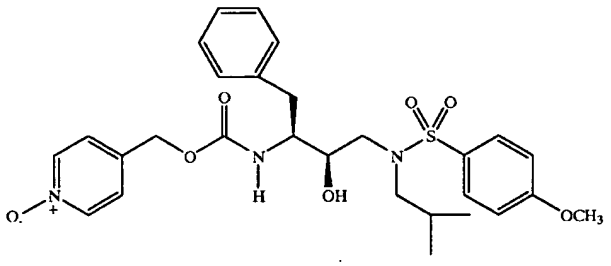
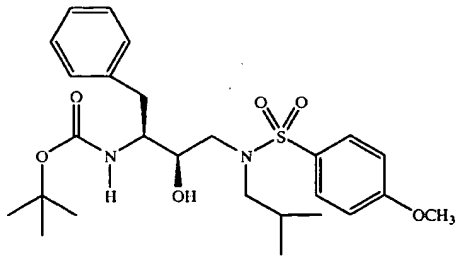
Entry	Compound	IC_{50} (nM)	EC_{50} (nM)	TD_{50} (nM)
23		2	8	
24		3		
25		60	120	167,000
26		68		
27		5	177	300,000

TABLE 21-continued

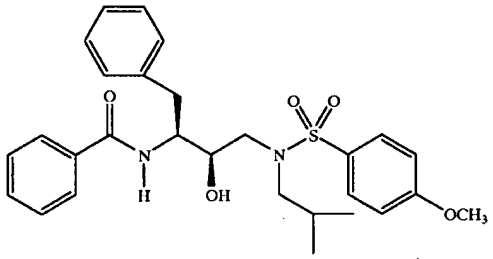
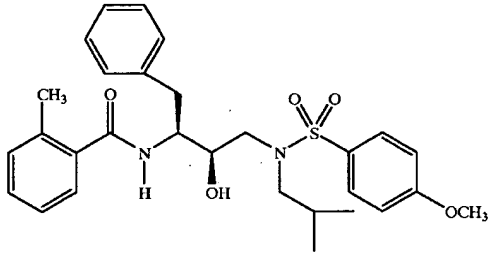
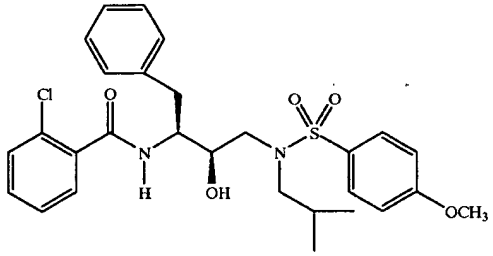
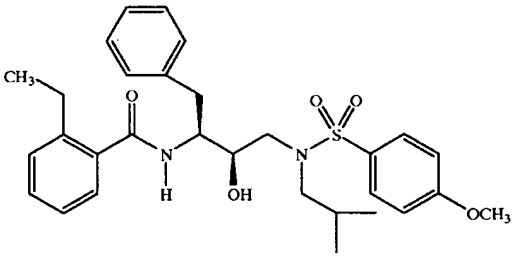
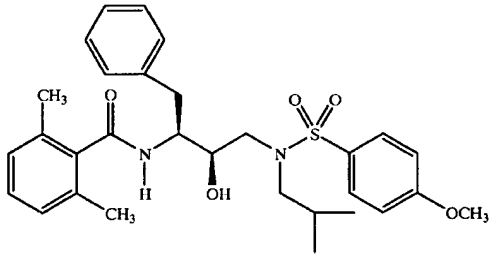
Entry	Compound	IC_{50} (nM)	EC_{50} (nM)	TD_{50} (nM)
28		14	76	213,000
29		5	105	196,000
30		6	154	154,000
31		10		
32		5	98	17,000

TABLE 21-continued

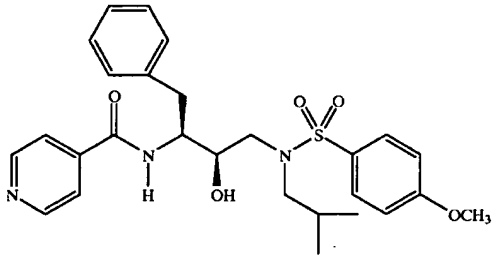
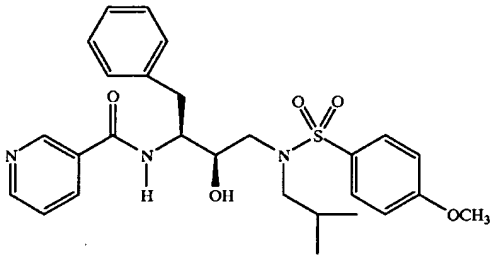
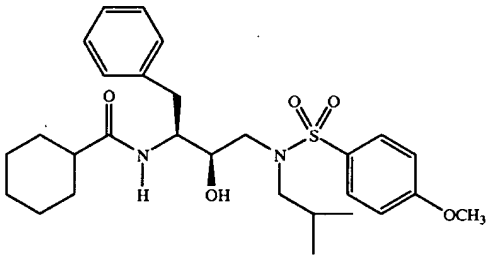
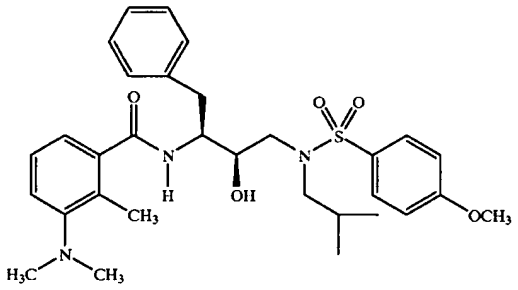
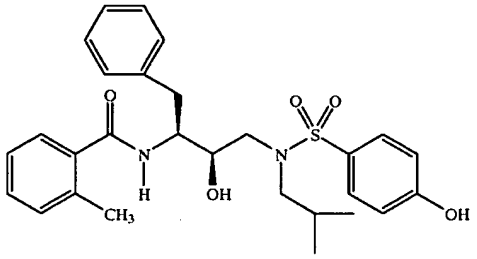
Entry	Compound	IC_{50} (nM)	EC_{50} (nM)	TD_{50} (nM)
33		18	68	
34		67	188	
35		18		
36		310	898	
37		7	<20	

TABLE 21-continued

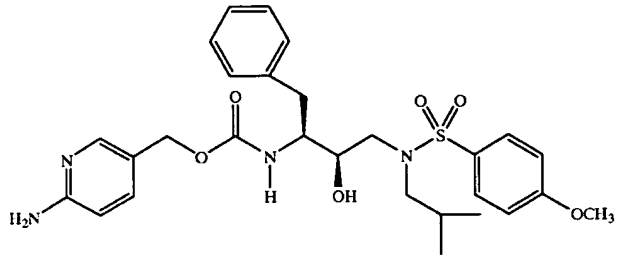
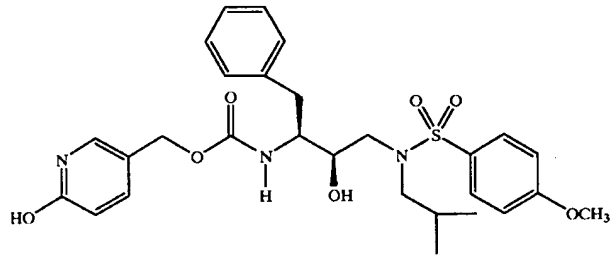
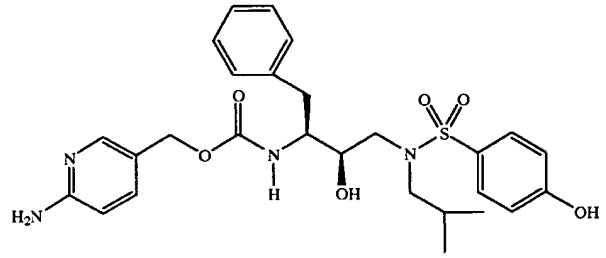
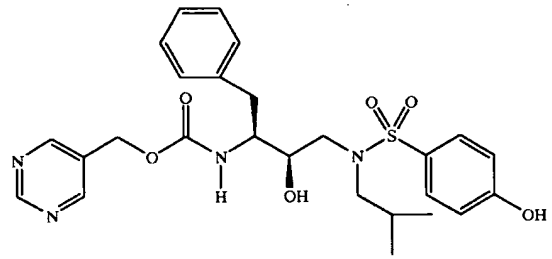
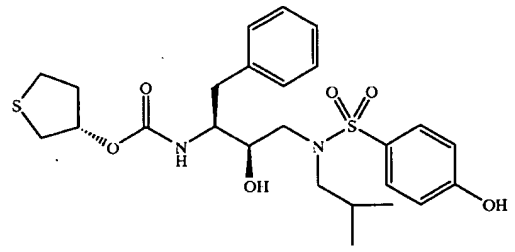
Entry	Compound	IC_{50} (nM)	EC_{50} (nM)	TD_{50} (nM)
38		4	1,100	
39		16	269	
40		3		
41		3	11	
42		2	<20	

TABLE 21-continued

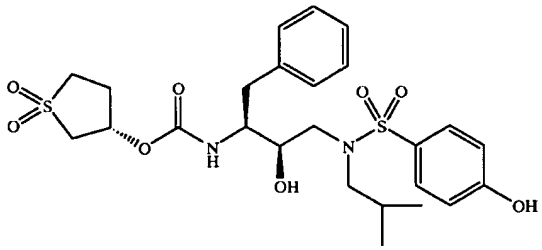
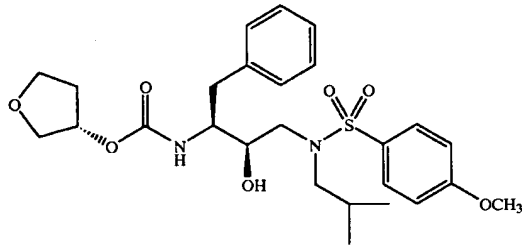
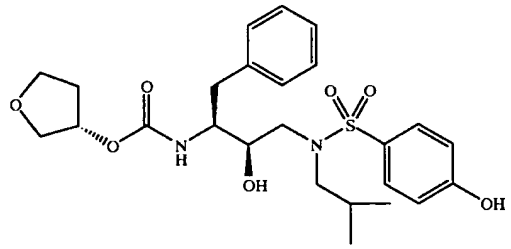
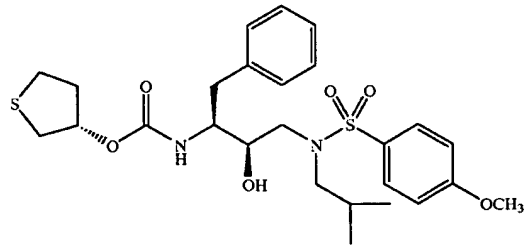
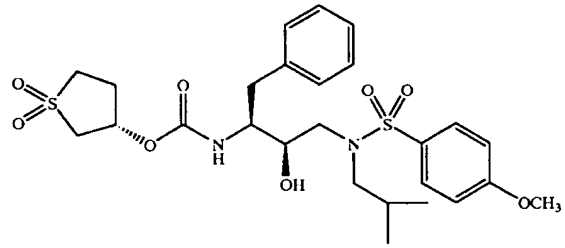
Entry	Compound	IC_{50} (nM)	EC_{50} (nM)	TD_{50} (nM)
43		4	63	
44		4	8	
45		2	5	
46		2	<20	
47		3	<20	

TABLE 21-continued

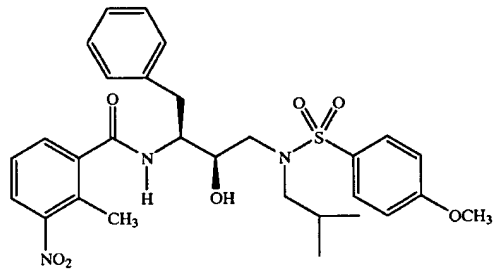
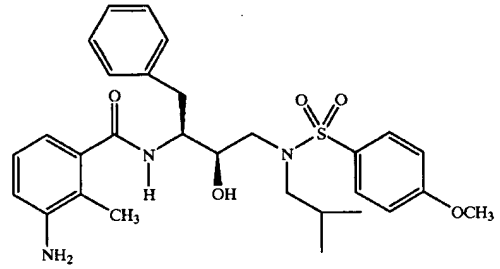
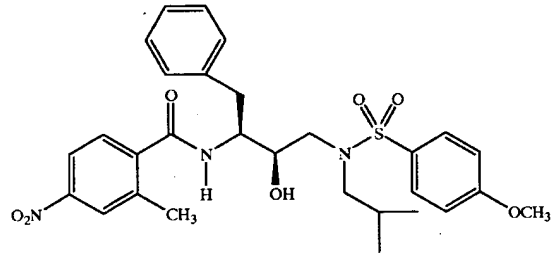
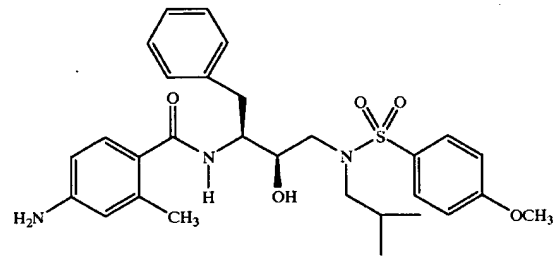
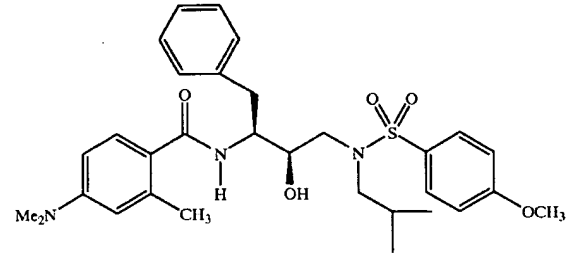
Entry	Compound	IC_{50} (nM)	EC_{50} (nM)	TD_{50} (nM)
48		17	210	
49		6	<20	
50		14		
51		9	<20	
52		>100		

TABLE 21-continued

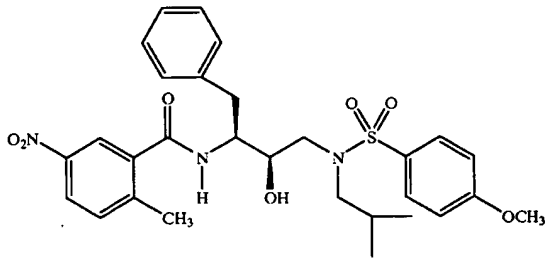
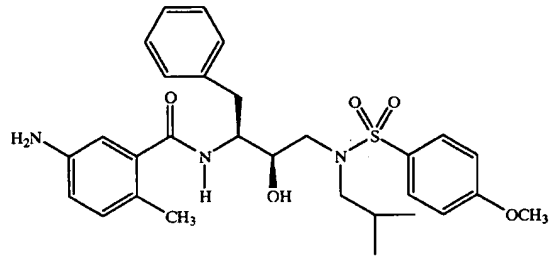
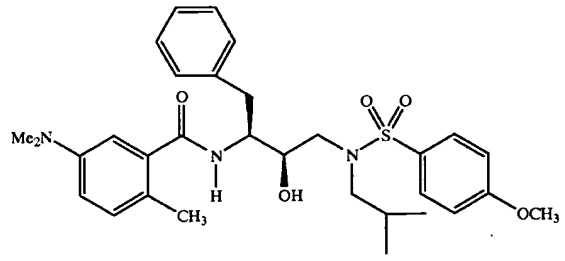
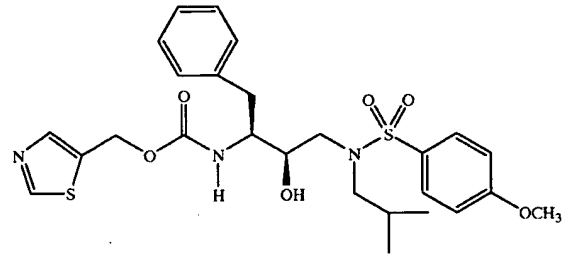
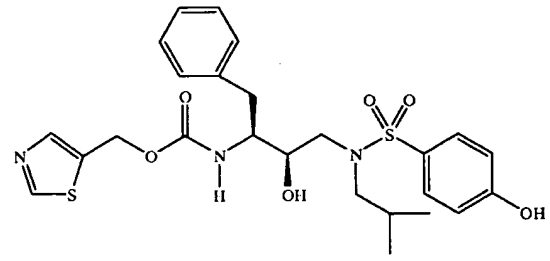
Entry	Compound	IC_{50} (nM)	EC_{50} (nM)	TD_{50} (nM)
53		21		
54		10		
55		37		
56		4	40	
57		4	<20	

TABLE 21-continued

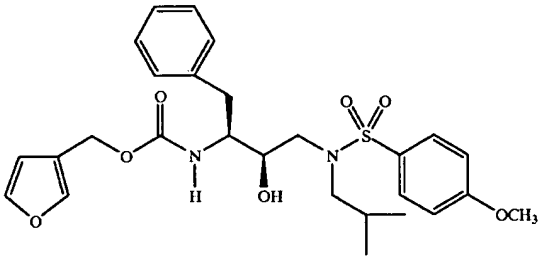
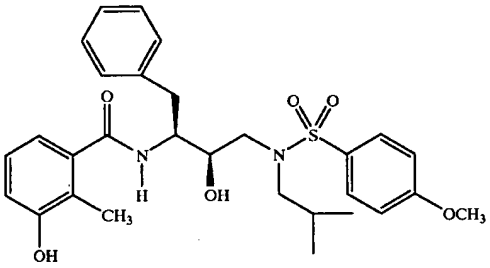
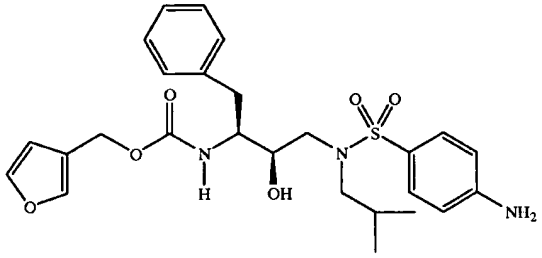
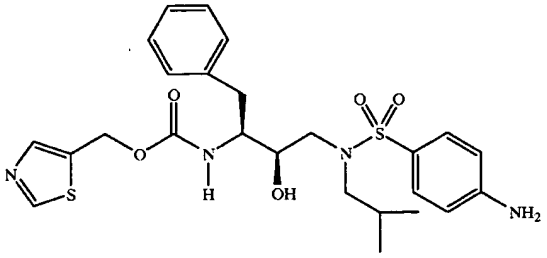
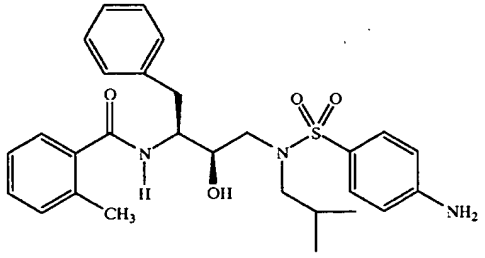
Entry	Compound	IC_{50} (nM)	EC_{50} (nM)	TD_{50} (nM)
58		2	70	
59		3	22	
60		5	60	
61		16		
62		28		

TABLE 21-continued

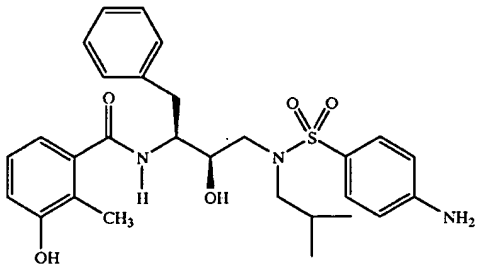
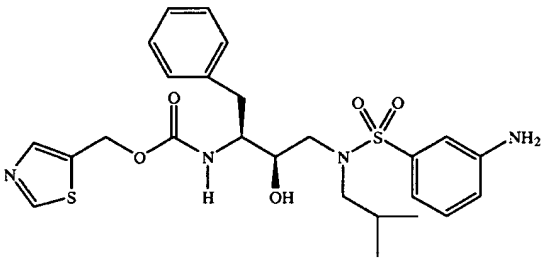
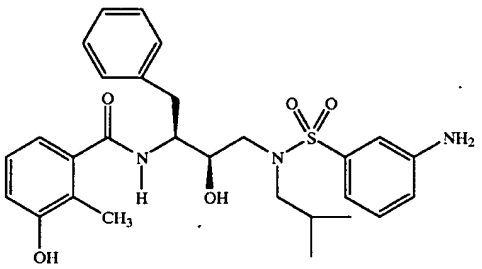
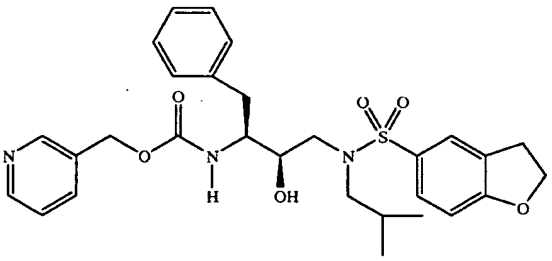
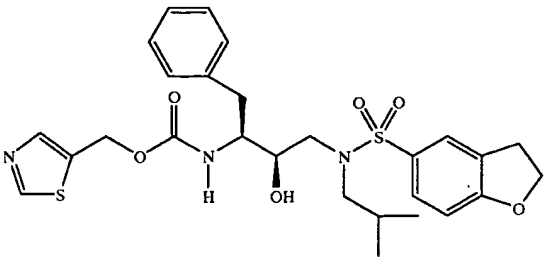
Entry	Compound	IC_{50} (nM)	EC_{50} (nM)	TD_{50} (nM)
63		7		
64		7		
65		4		
66		4		
67		5		

TABLE 21-continued

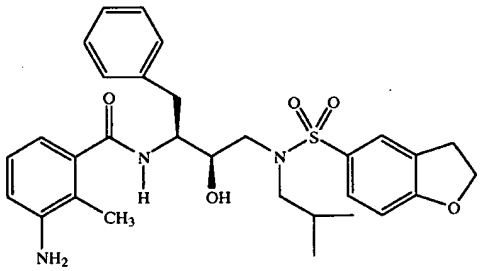
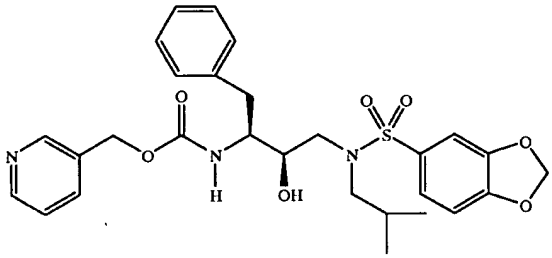
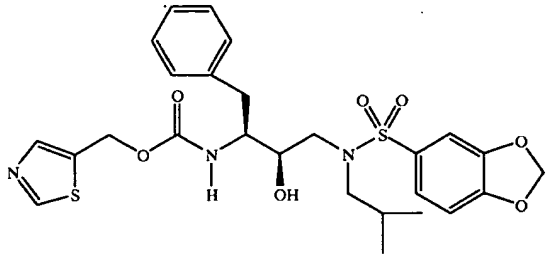
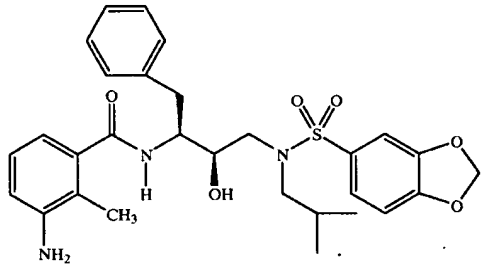
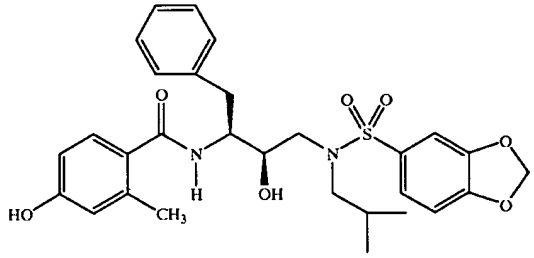
Entry	Compound	IC_{50} (nM)	EC_{50} (nM)	TD_{50} (nM)
68		7		
69		4	68	
70		5	30	
71		5		
72		5	42	

TABLE 21-continued

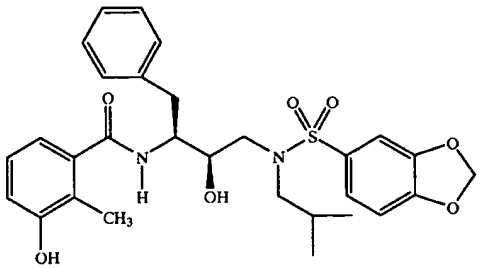
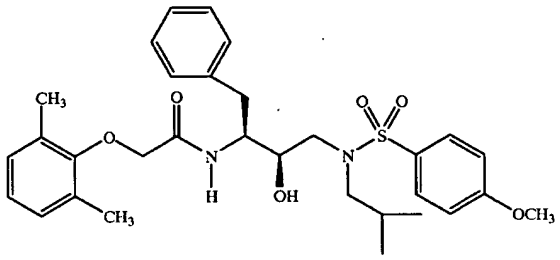
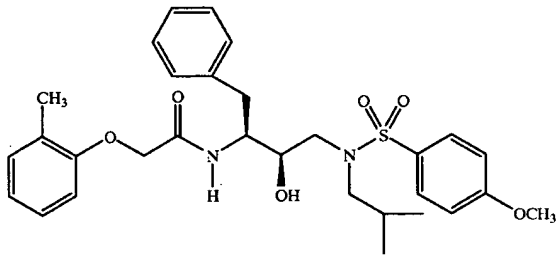
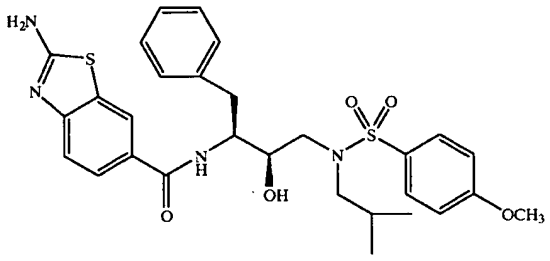
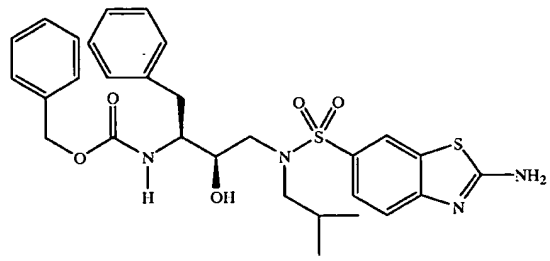
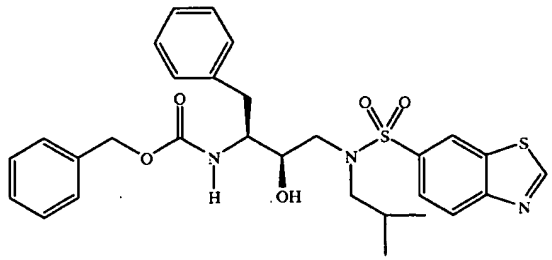
Entry	Compound	IC_{50} (nM)	EC_{50} (nM)	TD_{50} (nM)
73		4	22	
74		3		
75		8		
76		5		
77		2		

TABLE 21-continued

Entry	Compound	IC_{50} (nM)	EC_{50} (nM)	TD_{50} (nM)
78		3		

The compounds of the present invention are effective antiviral compounds and, in particular, are effective retroviral inhibitors as shown above. Thus, the subject compounds are effective HIV protease inhibitors. It is contemplated that the subject compounds will also inhibit other retroviruses such as other lentiviruses in particular other strains of HIV, e.g. HIV-2, human T-cell leukemia virus, respiratory syncitial virus, simia immunodeficiency virus, feline leukemia virus, feline immuno-deficiency virus, hepadnavirus, cytomegalovirus and picornavirus. Thus, the subject compounds are effective in the treatment and/or proplylaxis of retroviral infections.

The subject compounds are also effective in preventing the growth of retroviruses in a solution. Both human and animal cell cultures, such as T-lymphocyte cultures, are utilized for a variety of well known purposes, such as research and diagnostic procedures including calibrators and controls. Prior to and during the growth and storage of a cell culture, the subject compounds may be added to the cell culture medium at an effective concentration to prevent the unexpected or undesired replication of a retrovirus that may inadvertently or unknowingly be present in the cell culture. The virus may be present originally in the cell culture, for example HIV is known to be present in human T-lymphocytes long before it is detectable in blood, or through exposure to the virus. This use of the subject compounds prevents the unknowing or inadvertent exposure of a potentially lethal retrovirus to a researcher or clinician.

Compounds of the present invention can possess one or more asymmetric carbon atoms and are thus capable of existing in the form of optical isomers as well as in the form of racemic or nonracemic mixtures thereof. The optical isomers can be obtained by resolution of the racemic mixtures according to conventional processes, for example by formation of diastereoisomeric salts by treatment with an optically active acid or base. Examples of appropriate acids are tartaric, diacetyltartaric, dibenzoyltartaric, ditoluoyltartaric and camphorsulfonic acid and then separation of the mixture of diastereoisomers by crystallization followed by liberation of the optically active bases from these salts. A different process for separation of optical isomers involves the use of a chiral chromatography column optimally chosen to maximize the separation of the enantiomers. Still another available method involves synthesis of covalent diastereoisomeric molecules by reacting compounds of Formula I with an optically pure acid in an activated form or an optically pure isocyanate. The synthesized diastereoisomers can be separated by conventional means such as chromatography, distillation, crystallization or sublimation, and then hydrolyzed to deliver the enantiomerically pure compound. The optically active compounds of Formula I can likewise be obtained by utilizing optically active starting materials. These isomers may be in the form of a free acid, a free base, an ester or a salt.

The compounds of the present invention can be used in the form of salts derived from inorganic or organic acids. These salts include but are not limited to the following: acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, cyclopentanepropionate, dodecylsulfate, ethanesulfonate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxy-ethanesulfonate, lactate, maleate, methanesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, palmoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate, mesylate and undecanoate. Also, the basic nitrogen-containing groups can be quaternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides, and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl, and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides, and others. Water or oil-soluble or dispersible products are thereby obtained.

Examples of acids which may be employed to form pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid, sulphuric acid and phosphoric acid and such organic acids as oxalic acid, maleic acid, succinic acid and citric acid. Other examples include salts with alkali metals or alkaline earth metals, such as sodium, potassium, calcium or magnesium or with organic bases.

Total daily dose administered to a host in single or divided doses may be in amounts, for example, from 0.001 to 10 mg/kg body weight daily and more usually 0.01 to 1 mg. Dosage unit compositions may contain such amounts of submultiples thereof to make up the daily dose.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration.

The dosage regimen for treating a disease condition with the compounds and/or compositions of this invention is selected in accordance with a variety of factors, including the type, age, weight, sex, diet and medical condition of the patient, the severity of the disease, the route of administration, pharmacological considerations such as the

activity, efficacy, pharmacokinetic and toxicology profiles of the particular compound employed, whether a drug delivery system is utilized and whether the compound is administered as part of a drug combination. Thus, the dosage regimen actually employed may vary widely and therefore may deviate from the preferred dosage regimen set forth above.

The compounds of the present invention may be administered orally, parenterally, by inhalation spray, rectally, or topically in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles as desired. Topical administration may also involve the use of transdermal administration such as transdermal patches or iontophoresis devices. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection, or infusion techniques.

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Suppositories for rectal administration of the drug can be prepared by mixing the drug with a suitable nonirritating excipient such as cocoa butter and polyethylene glycols which are solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum and release the drug.

Solid dosage forms for oral administration may include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound may be admixed with at least one inert diluent such as sucrose lactose or starch. Such dosage forms may also comprise, as in normal practice, additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

Liquid dosage forms for oral administration may include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions may also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

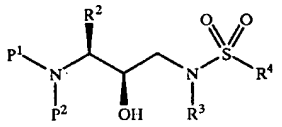
While the compounds of the invention can be administered as the sole active pharmaceutical agent, they can also be used in combination with one or more immunomodulators, antiviral agents or other antiinfective agents. For example, the compounds of the invention can be administered in combination with AZT, DDI, DDC or with glucosidase inhibitors, such as N-butyl-1-deoxynojirimycin or prodrugs thereof, for the prophylaxis and/or treatment of AIDS. When administered as a combination, the therapeutic agents can be formulated as separate compositions which are given at the same time or different times, or the therapeutic agents can be given as a single composition.

The foregoing is merely illustrative of the invention and is not intended to limit the invention to the disclosed compounds. Variations and changes which are obvious to one skilled in the art are intended to be within the scope and nature of the invention which are defined in the appended claims.

From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

What is claimed is:

1. A compound represented by the formula:



or a pharmaceutically acceptable salt, prodrug, or ester thereof, wherein

P^1 represents alkoxycarbonyl, aralkoxycarbonyl, alkylcarbonyl, cycloalkylcarbonyl, cycloalkylalkoxycarbonyl, cycloalkylalkanoyl, alkanoyl, aralkanoyl, aroyl, aryloxycarbonyl, aryloxycarbonylalkyl, aryloxyalkanoyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, heterocyclylalkanoyl, heterocyclylalkoxycarbonyl, heteroaralkanoyl, heteroaralkoxycarbonyl, heteroaryloxycarbonyl, heteroaroyl, alkyl, alkenyl, cycloalkyl, aryl, aralkyl, aryloxyalkyl, heteroaryloxyalkyl, hydroxyalkyl, aminocarbonyl, aminoalkanoyl, and mono- and disubstituted aminocarbonyl and mono- and disubstituted aminoalkanoyl radical wherein the substituents are selected from the group consisting of alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, and heterocycloalkyalkyl radicals; or where said aminoalkanoyl radicals is disubstituted, said substituents along with the nitrogen atom to which they are attached form a heterocycloalkyl or heteroaryl radical;

P^2 is hydrogen;

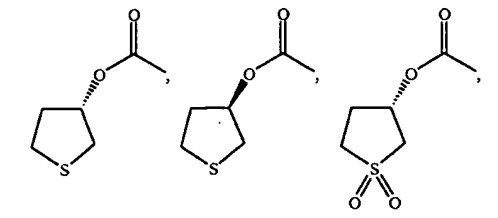
R^2 is an alkyl, aryl, cycloalkyl, cycloalkylalkyl or aralkyl radical, which radicals are optionally substituted with a group selected from alkyl and halogen radicals, nitro, cyano, CF_3, —OR^9, —SR^9, wherein R^9 is a hydrogen, alkyl or halogen radical;

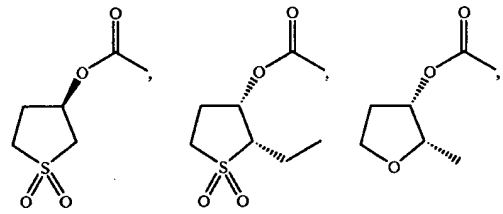
R^3 is a hydrogen, alkyl, haloalkyl alkenyl, alkynyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heteroaryl, heterocycloalkylalkyl, aryl, aralkyl, heteroaralkyl, aminoalkyl or mono- or disubstituted aminoalkyl radical, wherein said substituents are selected from the group consisting of alkyl, aryl, arakyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, and heterocycloalkylalkyl radicals, or where the aminoalkyl radical is disubstituted, said substituents along with the nitrogen atom to which they are attached, form a heterocycloalkyl or a heteroaryl radical; and

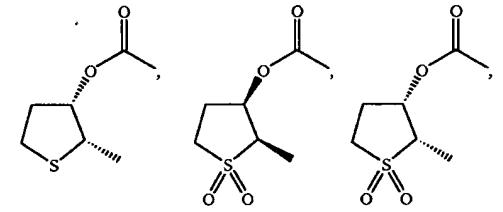
R^4 is a radical as defined by R^3 except for hydrogen.

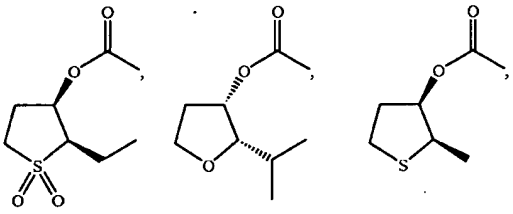
2. A compound of claim 1 wherein P^1 is heteroclyloxycarbonyl.

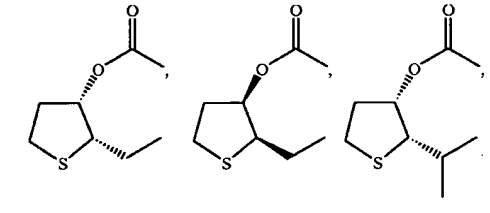
3. A compound of claim 2 wherein the heterocycloxycarbonyl is selected from the following:

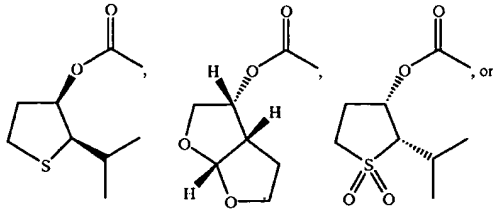




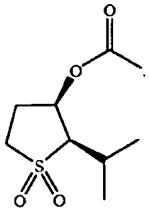




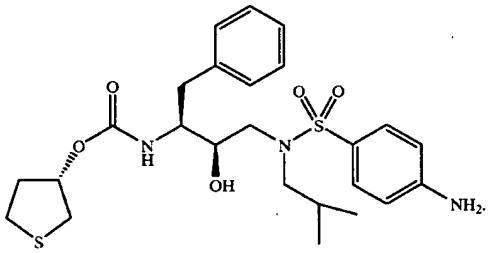




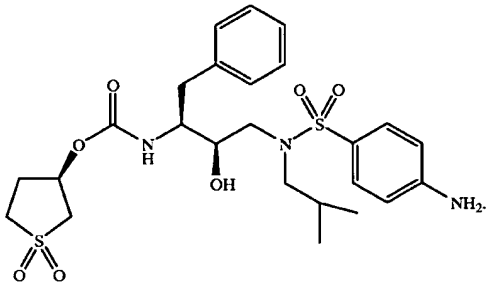
-continued



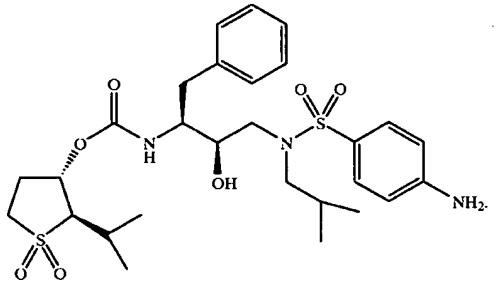
4. A compound of claim **3** which is:



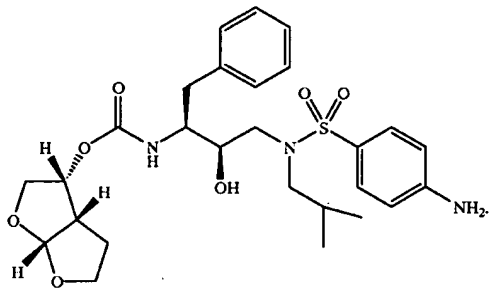
5. A compound of claim **3** which is:



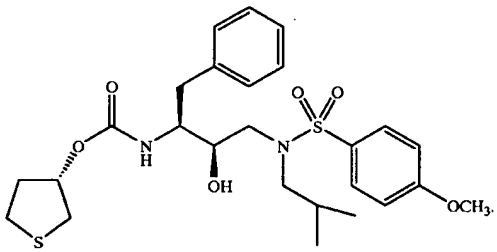
6. A compound of claim **3** which is:



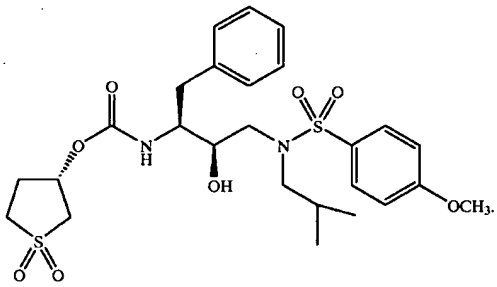
7. A compound of claim 3 which is:



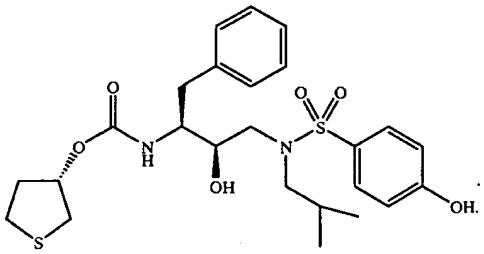
8. A compound of claim 3 which is:



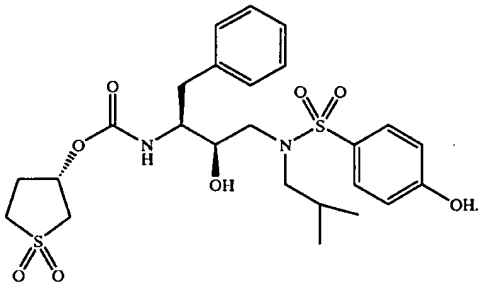
9. A compound of claim 3 which is:



10. A compound of claim 3 which is:



11. A compound of claim 3 which is:



12. Method of treating a retroviral infection comprising administering an effective amount of a compound of claim 2.

13. A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier.

14. Method of inhibiting a retrovirus protease comprising administering a protease inhibiting amount of a composition of claim 13.

15. Method of claim 14 wherein the retrovirals protease is HIV protease.

16. Method of treating a retrovirus infection comprising administering an effective amount of a composition of claim 13.

17. Method of claim 16 wherein the retrovirals infection is an HIV infection.

18. Method for treating AIDS comprising administering an effective amount of a composition of claim 13.

* * * * *

Exhibit 4

Copy of U.S. Patent & Trademark Office Maintenance Fee Statement for U.S. Patent No. 6,248,775

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

Customer Num: 000000

FRANK S UNGEMACH
G D SEARLE & CO
CORPORATE PATENT LAW DEPARTMENT
P O BOX 5110
CHICAGO IL 60680-9889

MAINTENANCE FEE STATEMENT

The data shown below is from the records of the U.S. Patent and Trademark Office. If the maintenance fee and any necessary surcharge have been timely paid for the patent listed below, the notation "PAID" will appear in the "STAT" column.

If the statement of small entity status is defective the reason will be indicated below in the "Small Entity" status column. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

PATENT NUMBER	FEE AMT	SUR CHARGE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	STAT	ATTY DKT NUMBER
6,248,775	**$910.00**	**$0.00**	**09/288,080**	**06/19/01**	**04/08/99**	**04**	**NO**	**PAID**	**1765.80234**

Direct any questions about this notice to:
Mail Stop M Correspondence
Director of the U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

Exhibit 5

Terminal Disclaimer filed in U.S. Patent No. 6,248,775

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT of	)	Original Group Art Unit: 1626
	)	
VAZQUEZ *et al.*	)	Examiner: D. Lambkin
	)	
Patent No. 6,248,775	)	
	)	
Issued: June 19, 2001	)	
	)	
Serial No. 09/288,080	)	
	)	
Filed: April 8, 1999	)	Atty. Dkt. No. 01765.80234 (2705/10)

For: **α- and β-Amino Acid Hydroxyethylamino Sulfonamides Useful As Retroviral Protease Inhibitors**

TERMINAL DISCLAIMER 37 C.F.R. § 1.321(a)

Assistant Commissioner of Patents
Washington, DC 20231

Sir:

In accordance with 37 C.F.R. 1.321(a), the sole owner of the complete interest in the subject patent, G.D. Searle & Co. (now identified as G.D. Searle LLC), hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the subject application, which would extend beyond the expiration date of the full statutory term defined in 35 U.S.C. 154 to 156 and 173 of U.S. Patents 5,843,946; 5,968,942; 6,046,190 and 6,060,476. G.D. Searle & Co. (now identified as G.D. Searle LLC), hereby agrees that the subject patent shall be enforceable only for and during such period that said patent and U.S. Patents 5,843,946; 5,968,942; 6,046,190 and 6,060,476 remain commonly owned. This agreement runs with the subject patent and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of the subject patent that would extend to the earliest expiration date of the full statutory term, as defined in 35 U.S.C. 154 to 156 and 173, of U.S. Patents 5,843,946; 5,968,942; 6,046,190 and 6,060,476, in the event that any one or more of such patents: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or is terminally disclaimed under 37 C.F.R. 1.321, has all claims canceled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of their full statutory terms as shortened by any terminal disclaimers filed prior to their grant.

The undersigned is an Attorney of Record.

The Commissioner also is authorized to charge the requisite fee of 37 C.F.R. § 1.20(d) (believed to be $110.00) to our Deposit Account No. 19-0733.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

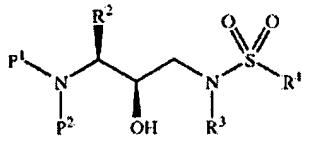
Date: August 17, 2001

By: _____
Joseph M. Skerpon (Reg. No.29,864)
Attorney of Record

Exhibit 6

Claims 3 and 7 of U.S. Patent No. 6,248,775 Claims the Active Ingredient of the Approved Product

1. A compound represented by the formula:



or a pharmaceutically acceptable salt, prodrug, or ester thereof, wherein

P^1 represents alkoxycarbonyl, aralkoxycarbonyl, alkylcarbonyl, cycloalkylcarbonyl, cycloalkylalkoxycarbonyl, cycloalkylalkanoyl, alkanoyl, aralkanoyl, aroyl, aryloxycarbonyl, aryloxycarbonylalkyl, aryloxyalkanoyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, heterocyclylalkanoyl, heterocyclylalkoxycarbonyl, heteroaralkanoyl, heteroaralkoxycarbonyl, heteroaryloxycarbonyl, heteroaroyl, alkyl, alkenyl, cycloalkyl, aryl, aralkyl, aryloxyalkyl, heteroaryloxyalkyl, hydroxyalkyl, aminocarbonyl, aminoalkanoyl, and mono- and disubstituted aminocarbonyl and mono- and disubstituted aminoalkanoyl radical wherein the substituents are selected from the group consisting of alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, and heterocycloalkyalkyl radicals; or where said aminoalkanoyl radicals is disubstituted, said substituents along with the nitrogen atom to which they are attached form a heterocycloalkyl or heteroaryl radical;

P^2 is hydrogen;

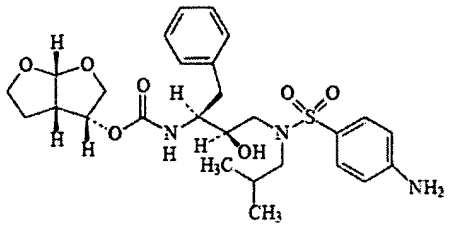
R^2 is an alkyl, aryl, cycloalkyl, cycloalkylalkyl or aralkyl radical, which radicals are optionally substituted with a group selected from alkyl and halogen radicals, nitro, cyano, CF_3, —OR^9, —SR^9, wherein R^9 is a hydrogen, alkyl or halogen radical;

R^3 is a hydrogen, alkyl, haloalkyl alkenyl, alkynyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heteroaryl, heterocycloalkylalkyl, aryl, aralkyl, heteroaralkyl, aminoalkyl or mono- or disubstituted aminoalkyl radical, wherein said substituents are selected from the group consisting of alkyl, aryl, arakyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, and heterocycloalkylalkyl radicals, or where the aminoalkyl radical is disubstituted, said substituents along with the nitrogen atom to which they are attached, form a heterocycloalkyl or a heteroaryl radical; and

R^4 is a radical as defined by R^3 except for hydrogen.

2. A compound of claim 1 wherein P^1 is heterocyloxycarbonyl.

The chemical structure of darunavir is:



Darunavir is covered by the chemical structure set forth in Claim 3 (dependent on claim 2, which is dependent on claim 1), wherein:

P^1 is heterocyclyloxycarbonyl

P^2 is hydrogen;

R^2 is aralkyl;

R^3 is alkyl;

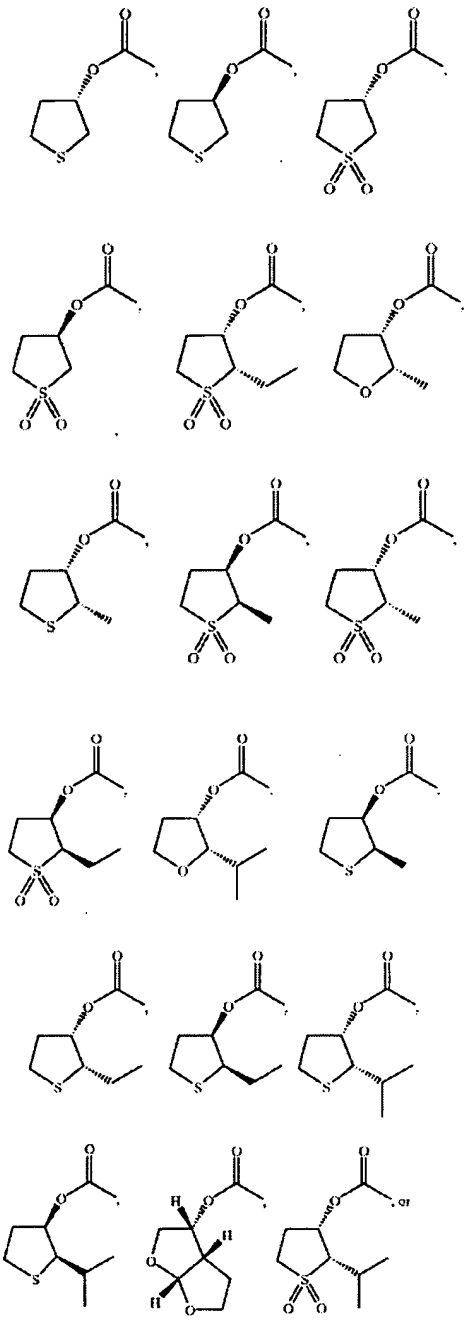
R^4 is aryl substituted with amino.;

See Column 10, lines 4-20, defining "aryl" to include substitutions:

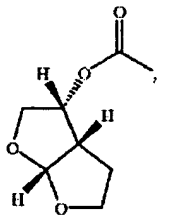
The term "aryl", alone or in combination, means a phenyl or naphthyl radical which optionally carries one or more substituents selected from alkyl, alkoxy, halogen, hydroxy, amino, nitro, cyano, haloalkyl, carboxy, alkoxycarbonyl, cycloalkyl, heterocycloalkyl, amido, mono and dialkyl substituted amino, mono and dialkyl substituted amido and the like, such as phenyl, p-tolyl, 4-methoxyphenyl, 4-(tert-butoxy)phenyl, 3-methyl-4-methoxyphenyl, 4-fluorophenyl, 4-chlorophenyl, 3-nitrophenyl, 3-aminophenyl, 3-acetamidophenyl, 4-acetamidophenyl, 2-methyl-3-acetamidophenyl, 2-methyl-3-aminophenyl, 3-methyl-4-aminophenyl, 2-amino-3-methylphenyl, 2,4-dimethyl-3-aminophenyl, 4-hydroxyphenyl, 3-methyl-4-hydroxyphenyl, 1-naphthyl, 2-naphthyl, 3-amino-1-naphthyl, 2-methyl-3-amino-1-naphthyl, 6-amino-2-naphthyl, 4,6-dimethoxy-2-naphthyl and the like.

P^1 is heterocyclyloxycarbonyl

3. A compound of claim 2 wherein the heterocycloxycarbonyl is selected from the following:



wherein the heterocyclyloxycarbonyl is:



The claim to the compound represented by the formula encompasses both darunavir and darunavir ethanolate.

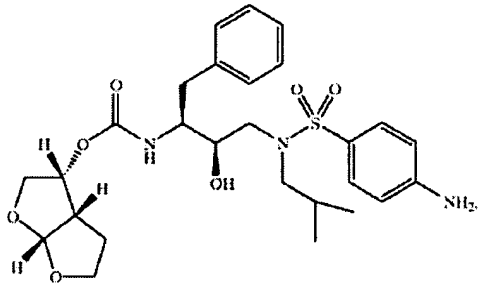
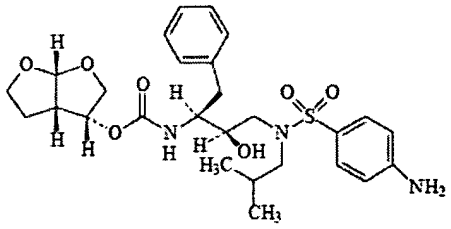
7. A compound of claim 3 which is: 	**The compound of claim 7 is darunavir:**  **The claim to the compound represented by the formula encompasses both darunavir and darunavir ethanolate.**

Exhibit 7

DESCRIPTION OF SIGNIFICANT ACTIVITIES OF APPLICANT DURING REGULATORY REVIEW

IND 62,477 (Darunavir) US Submission Log

Date	Serial Number	Submission
12/19/2002	000	Original Investigational New Drug Application
4/4/2003	001	Request for Comments on draft protocol TMC114-C202
4/11/2003	002	Protocol Amendment-Change in Protocol TMC114-C133 Response to FDA Request for Information
5/29/2003	003	Sponsor Name & Address Change
5/30/2003	004	General Correspondence
6/6/2003	005	Meeting Request (Type B)
6/10/2003	006	Protocol Amendment - New Investigator TMC114-C133
7/11/2003	007	Response to FDA Request for information Information Amendment – Chemistry, Manufacturing and Controls; Pharmacology/Toxicology
7/14/2003	008	Information Amendment – Clinical Investigator's Brochure
7/15/2003	009	Response to FDA Comments on draft Protocol TMC114-C202
7/15/2003	010	Briefing Package - August 6, 2003 Type B Meeting
8/12/2003	011	IND Safety Report: Initial
8/20/2003	012	Protocol Amendment - Change in Protocol TMC114-C133
8/22/2003	013	Protocol Amendment - New Protocol TMC114-C202
8/25/2003	014	General Correspondence - Study protocol TMC114-C213
8/28/2003	015	IND Safety Report: Initial
9/5/2003	016	Information Amendment - Pharmacology/Toxicology; Clinical
9/15/2003	017	General Correspondence
9/17/2003	018	General Correspondence
9/30/2003	019	IND Safety Report: Follow up (F/U)
10/3/2003	020	Information Amendment - Chemistry, Manufacturing and Controls
10/31/2003	021	Protocol Amendment - New Investigator TMC114-C202
11/6/2003	022	Protocol Amendment - New Protocol TMC114-C215
11/14/2003	023	General Correspondence
11/21/2003	024	General Correspondence
11/26/2003	025	Response to FDA Request for Information
12/9/2003	026	Protocol Amendment - New Investigator TMC114-C202
1/9/2004	027	Protocol Amendment - New Protocol TMC114-C149
1/22/2004	028	IND Safety Report: Initial
1/26/2004	029	IND Safety Report: Initial
2/2/2004	030	Protocol Amendment - New Protocol TMC114-C128
2/3/2004	031	Information Amendment - Chemistry, Manufacturing and Controls
2/6/2004	032	IND Safety Report: Initial
2/11/2004	033	Protocol Amendment - New Investigator TMC114-C202
2/12/2004	034	General Correspondence
2/13/2004	035	IND Safety Report: Initial
2/20/2004	036	IND Safety Report: Initial
2/24/2004	037	Protocol Amendment - New Protocol TMC114-C122
2/25/2004	038	Information Amendment - Chemistry, Manufacturing and Controls

Date	Serial Number	Submission
2/26/2004	039	Protocol Amendment - Change in Protocol TMC114-C202
2/27/2004	040	Protocol Amendment - Change in Protocol TMC114-C149
3/3/2004	041	Response to FDA Request for Information
3/5/2004	042	IND Safety Report: Initial
3/8/2004	043	IND Safety Report: Initial
3/10/2004	044	Response to FDA Comments Protocol TMC114-C215
3/11/2004	045	IND Safety Report: Initial
3/15/2004	046	IND Safety Report: F/U(s)
3/16/2004	047	IND Safety Report: F/U(s)
3/16/2004	048	IND Safety Report: Initial
3/17/2004	049	IND Safety Report: Initial
3/17/2004	050	Information Amendment - Pharmacology/Toxicology
3/18/2004	051	IND Safety Report: Initial & F/U(s)
3/19/2004	052	Response to FDA Request for Information
3/19/2004	053	IND Annual Report
3/22/2004	054	IND Safety Report: Initial
3/26/2004	055	IND Safety Report: Initial
3/31/2004	056	IND Safety Report: Initial
4/1/2004	057	IND Safety Report: F/U(s)
4/2/2004	058	General Correspondence
4/7/2004	059	IND Safety Report: Initial
4/8/2004	060	IND Safety Report: Initial
4/9/2004	061	IND Safety Report: Initial
4/12/2004	062	IND Safety Report: Initial
4/13/2004	063	IND Safety Report: F/U(s)
4/14/2004	064	IND Safety Report: Initial
4/16/2004	065	IND Safety Report: F/U(s)
4/20/2004	066	IND Safety Report: Initial
4/21/2004	067	IND Safety Report: Initial
4/26/2004	068	IND Safety Report: Initial
4/28/2004	069	IND Safety Report: Initial
4/30/2004	070	Response to FDA Request for information
5/3/2004	071	IND Safety Report: F/U(s)
5/4/2004	072	IND Safety Report: Initial
5/5/2004	073	Protocol Amendment - New Protocol TMC114-C121
5/7/2004	074	Protocol Amendment - Change in Protocol TMC114-C149
5/10/2004	075	IND Safety Report: Initial
5/12/2004	076	Information Amendment - Chemistry, Manufacturing and Controls
5/14/2004	077	Protocol Amendment - New Investigator TMC114-C202
5/19/2004	078	IND Safety Report: Initial
5/20/2004	079	Protocol Amendment - New Investigator TMC114-C149
5/24/2004	080	Response to FDA Request for Information
6/1/2004	081	IND Safety Report: Initial
6/2/2004	082	IND Safety Report: F/U(s)
6/3/2004	083	Protocol Amendment - Change in Protocol TMC114-C202
6/3/2004	084	Response to FDA Request for Information
6/4/2004	085	Protocol Amendment - New Protocol TMC114-C141
6/7/2004	086	General Correspondence
6/8/2004	087	IND Safety Report: F/U(s)
6/8/2004	088	Protocol Amendment - New Investigator TMC114-C215

Date	Serial Number	Submission
6/10/2004	089	Information Amendment - Chemistry, Manufacturing and Controls
6/10/2004	090	General Correspondence
6/10/2004	091	IND Safety Report: F/U(s)
6/14/2004	092	Protocol Amendment - New Investigator TMC114-C122
6/17/2004	093	IND Safety Report: Initial
6/18/2004	094	General Correspondence
6/23/2004	095	General Correspondence
6/25/2004	096	IND Safety Report: F/U(s)
6/29/2004	097	IND Safety Report: F/U(s)
6/30/2004	098	IND Safety Report: F/U(s)
6/30/2004	099	General Correspondence
7/1/2004	100	General Correspondence
7/6/2004	101	IND Safety Report: Initial & F/U(s)
7/7/2004	102	IND Safety Report: F/U(s)
7/8/2004	103	IND Safety Report: F/U(s)
7/14/2004	104	IND Safety Report: F/U(s)
7/15/2004	105	General Correspondence
7/16/2004	106	IND Safety Report: F/U(s)
7/19/2004	107	Protocol Amendment - Change in Protocol TMC114-C215
7/20/2004	108	IND Safety Report: F/U(s)
7/22/2004	109	IND Safety Report: F/U(s)
7/22/2004	110	General Correspondence
7/26/2004	111	Investigator's Brochure (Edition 5)
7/28/2004	113	Response to FDA Request for Information
7/29/2004	114	General Correspondence
7/30/2004	115	IND Safety Report: Initial
8/5/2004	116	IND Safety Report: Initial & F/U(s)
8/10/2004	117	IND Safety Report: Initial
8/11/2004	118	IND Safety Report: F/U(s)
8/12/2004	119	General Correspondence
8/16/2004	120	IND Safety Report: F/U(s)
8/18/2004	121	IND Safety Report: Initial
8/19/2004	122	IND Safety Report: Initial
8/20/2004	123	Protocol Amendment - Change in Protocol TMC114-C202
8/23/2004	124	IND Safety Report: F/U(s)
8/24/2004	125	IND Safety Report: Initial
8/24/2004	126	IND Safety Report: Initial
8/27/2004	127	Information Amendment - Pharmacology/Toxicology
9/1/2004	128	IND Safety Report: F/U(s)
9/2/2004	129	IND Safety Report: Initial
9/7/2004	130	IND Safety Report: Initial
9/7/2004	131	IND Safety Report: Initial
9/8/2004	132	IND Safety Report: Initial
9/9/2004	133	IND Safety Report: Initial
9/10/2004	134	General Correspondence
9/13/2004	135	IND Safety Report: Initial
9/16/2004	136	IND Safety Report: Initial
9/17/2004	137	Meeting Request
9/20/2004	138	IND Safety Report: Initial
9/21/2004	139	IND Safety Report: F/U(s)

Date	Serial Number	Submission
9/27/2004	140	General Correspondence
9/29/2004	141	Protocol Amendment - New Investigator TMC114-C215
9/29/2004	142	IND Safety Report: Initial
9/30/2004	143	IND Safety Report: F/U(s)
10/1/2004	144	IND Safety Report: Initial
10/4/2004	145	IND Safety Report: F/U(s)
10/5/2004	146	IND Safety Report: Initial & F/U(s)
10/6/2004	147	IND Safety Report: F/U(s)
10/8/2004	148	Response to FDA Comments for Protocol TMC114-C141
10/11/2004	149	General Correspondence
10/11/2004	150	End of Phase II CMC Meeting Request
10/15/2004	151	Information Amendment- Clinical
10/15/2004	152	Briefing Package-November 3, 2004 Type C Meeting
10/20/2004	153	IND Safety Report: F/U(s)
10/25/2004	154	General Correspondence
10/25/2004	155	IND Safety Report: F/U(s)
10/26/2004	156	IND Safety Report: Initial & F/U(s)
10/26/2004	157	Protocol Amendment - New Investigator TMC114-C202
10/27/2004	158	Information Amendment-Pharmacology/Toxicology Notice of intent
10/29/2004	159	IND Safety Report: Initial & F/U(s)
11/3/2004	160	IND Safety Report: Initial & F/U(s)
11/5/2004	161	IND Safety Report: Initial & F/U(s)
11/8/2004	162	IND Safety Report: Initial
11/9/2004	163	IND Safety Report: Initial & F/U(s)
11/9/2004	164	Briefing Package- End of Phase II CMC Meeting
11/10/2004	165	IND Safety Report: Initial
11/12/2004	166	General Correspondence
11/16/2004	167	IND Safety Report: Initial
11/18/2004	168	IND Safety Report: F/U(s)
11/18/2004	169	General Correspondence
11/19/2004	170	IND Safety Report: F/U(s)
11/23/2004	171	IND Safety Report: Initial
11/29/2004	172	IND Safety Report: F/U(s)
12/2/2004	173	Request for Special Protocol Assessment - Draft Carcinogenicity Protocol for Review and Comment
12/2/2004	174	Request for Special Protocol Assessment - Draft Carcinogenicity Protocol for Review and Comment
12/2/2004	175	IND Safety Report: Initial
12/8/2004	176	IND Safety Report Initial & F/U(s)
12/13/2004	177	General Correspondence
12/13/2004	178	IND Safety Report: F/U
12/14/2004	179	IND Safety Report: Initial
12/16/2004	180	General Correspondence
12/16/2004	181	IND Safety Report: Initial & F/U(s)
12/20/2004	182	General Correspondence
12/21/2004	183	IND Safety Report: F/U(s)
12/22/2004	184	Protocol Amendment-Change in Protocol TMC114-C202
12/22/2004	185	Protocol Amendment-Change in Protocol TMC114-C215
12/23/2004	186	General Correspondence - Draft Protocol TMC114-C214

Date	Serial Number	Submission
12/24/2004	187	IND Safety Report: Initial & F/U(s)
12/27/2004	188	IND Safety Report: F/U(s)
12/29/2004	189	IND Safety Report: Initial & F/U(s)
12/30/2004	190	Protocol Amendment - New Investigator TMC114-C202
1/3/2005	191	IND Safety Report: Initial
1/4/2005	192	General Correspondence
1/13/2005	193	IND Safety Report: Initial
1/14/2005	194	Protocol Amendment - New Investigator TMC114-C202
1/18/2005	195	General Correspondence
1/20/2005	196	IND Safety Report: Initial & F/U(s)
1/21/2005	197	General Correspondence
1/21/2005	198	IND Safety Report: F/U(s)
1/24/2005	199	IND Safety Report: Initial
1/25/2005	200	IND Safety Report: F/U
1/26/2005	201	IND Safety Report: Initial & F/U(s)
1/27/2005	202	IND Safety Report: Initial F/U(s)
1/27/2005	203	Response to FDA Request for Information
1/28/2005	204	Response to Executive CAC Recommendations
1/28/2005	205	Information Amendment- Chemistry, Manufacturing and Controls
2/2/2005	206	IND Safety Report: F/U(s)
2/3/2005	207	IND Safety Report: F/U(s)
2/4/2005	208	IND Safety Report: F/U(s)
2/7/2005	209	General Correspondence
2/7/2005	210	IND Safety Report: Initial
2/8/2005	211	IND Safety Report: Initial
2/8/2005	212	Protocol Amendment-Change in Protocol TMC114-C202
2/8/2005	213	Protocol Amendment-Change in Protocol; New Investigator TMC114-C215
2/9/2005	214	IND Safety Report: Initial & F/U(s)
2/10/2005	215	IND Safety Report: F/U(s)
2/11/2005	216	IND Safety Report: F/U(s)
2/11/2005	217	IND Safety Report: Initial
2/14/2005	218	IND Safety Report: Initial
2/15/2005	219	IND Safety Report: Initial & F/U(s)
2/15/2005	220	General Correspondence
2/17/2005	221	IND Safety Report: Initial & F/U(s)
2/18/2005	222	Response to FDA Clinical Comments for Protocol Amendment TMC114-C202
2/18/2005	223	General Correspondence
2/22/2005	224	IND Safety Report: Initial
2/24/2005	225	General Correspondence
2/24/2005	226	IND Safety Report: F/U(s)
2/24/2005	227	Response to FDA Request for Information
3/2/2005	228	IND Safety Report: Initial
3/3/2005	229	General Correspondence
3/3/2005	230	Pre-NDA Meeting Request - Type B
3/3/2005	231	General Correspondence
3/7/2005	232	Protocol Amendment-New Investigator TMC114-C215
3/7/2005	233	Response to FDA Request for Information - Chemistry
3/8/2005	234	Information Amendment-Pharmacology/Toxicology
3/8/2005	235	Information Amendment-Microbiology

Date	Serial Number	Submission
3/9/2005	236	IND Safety Report: F/U(s)
3/10/2005	237	Investigator's Brochure (Edition 6)
3/11/2005	238	General Correspondence
3/15/2005	239	IND Safety Report: Initial & F/U(s)
3/16/2005	240	Protocol Amendment- New Investigator TMC114-C215
3/18/2005	241	IND Safety Report: Initial
3/18/2005	242	IND Annual Report
3/22/2005	243	Information Amendment-Clinical;
3/24/2005	244	IND Safety Report: F/U(s)
3/25/2005	245	Protocol Amendment-New Protocol; New Investigator TMC114-C214 Response to FDA comments
3/28/2005	246	Information Amendment-Clinical;
3/29/2005	247	IND Safety Report: F/U(s)
3/31/2005	248	Protocol Amendment-New Protocol; New Investigator TMC114-C131
4/1/2005	249	IND Safety Report: Initial
4/7/2005	250	IND Safety Report: Initial
4/7/2005	251	Information Amendment-Chemistry, Manufacturing and Controls
4/12/2005	252	Protocol Amendment-New Protocol; New Investigator TMC114-C150
4/13/2005	253	Information Amendment- Chemistry, Manufacturing and Controls
4/13/2005	254	IND Safety Report: Initial
4/14/2005	255	IND Safety Report: Initial
4/15/2005	256	IND Safety Report: F/U(s)
4/15/2005	257	Information Amendment - Clinical
4/19/2005	258	IND Safety Report: Initial & F/U(s)
4/20/2005	259	IND Safety Report: Initial & F/U(s)
4/21/2005	260	IND Safety Report: Initial & F/U(s)
4/21/2005	261	Response to FDA Request for Information- Chemistry
4/25/2005	262	IND Safety Report: Initial
4/26/2005	263	Protocol Amendment- New Investigator TMC114-C215
4/28/2005	264	IND Safety Report: Initial
4/28/2005	265	Protocol Amendment-New Protocol; New Investigator TMC114-C209
4/29/2005	266	IND Safety Report: Initial
5/3/2005	267	IND Safety Report: Initial & F/U(s)
5/4/2005	268	IND Safety Report: Initial
5/6/2005	269	Briefing Package- Pre-NDA Meeting
5/9/2005	270	Information Amendment-Clinical
5/9/2005	271	IND Safety Report: Initial
5/10/2005	272	IND Safety Report: F/U(s)
5/11/2005	273	IND Safety Report: Initial & F/U(s)
5/12/2005	274	Information Amendment-Clinical
5/13/2005	275	General Correspondence; Response to FDA comments
5/16/2005	276	IND Safety Report: Initial & F/U(s)
5/17/2005	277	IND Safety Report: Initial & F/U(s)
5/18/2005	278	Protocol Amendment-New Investigator TMC114-C202
5/18/2005	279	IND Safety Report: Initial & F/U(s)
5/20/2005	280	IND Safety Report: Initial
5/20/2005	281	Information Amendment-Clinical
5/24/2005	282	Protocol Amendment-New Investigator TMC114-C214
5/24/2005	283	IND Safety Report: Initial & F/U(s)
5/26/2005	284	IND Safety Report: F/U(s)

Date	Serial Number	Submission
5/27/2005	285	General Correspondence; Response to FDA Comments
5/31/2005	286	Information Amendment-Clinical;
6/2/2005	287	IND Safety Report: Initial & F/U(s)
6/3/2005	288	Information Amendment-Clinical;
6/3/2005	289	General Correspondence; Response to FDA Comments
6/6/2005	290	IND Safety Report: Initial & F/U(s)
6/9/2005	291	IND Safety Report: Initial & F/U(s)
6/9/2005	292	General Correspondence
6/9/2005	293	Response to FDA Request for information
6/10/2005	294	Information Amendment-Clinical
6/10/2005	295	IND Safety Report: Initial
6/13/2005	296	IND Safety Report: Initial
6/14/2005	297	IND Safety Report: F/U(s)
6/15/2005	298	IND Safety Report: F/U(s)
6/17/2005	299	IND Safety Report: F/U(s)
6/20/2005	300	Information Amendment-Clinical
6/20/2005	301	IND Safety Report: F/U(s)
6/20/2005	302	General Correspondence
6/21/2005	303	IND Safety Report: Initial & F/U(s)
6/22/2005	304	IND Safety Report: F/U(s)
6/24/2005	305	Information Amendment-Clinical
6/27/2005	306	Protocol Amendment-New Investigator TMC114-C215
6/28/2005	307	IND Safety Report: Initial & F/U(s)
6/30/2005	308	Information Amendment-Clinical
6/30/2005	309	IND Safety Report: Initial & F/U(s)
7/1/2005	310	IND Safety Report: Initial & F/U(s)
7/6/2005	311	IND Safety Report: Initial
7/6/2005	312	Information Amendment-Chemistry, Manufacturing and Controls
7/7/2005	313	IND Safety Report: Initial & F/U(s)
7/8/2005	314	General Correspondence
7/8/2005	315	Protocol Amendment-Change in Protocol TMC114-C131
7/11/2005	316	Protocol Amendment-New Investigator
7/11/2005	317	Response to FDA Request for information; General Correspondence
7/11/2005	318	IND Safety Report: Initial
7/13/2005	319	IND Safety Report: Initial & F/U(s)
7/14/2005	320	Information Amend-Clinical
7/14/2005	321	IND Safety Report: F/U
7/15/2005	322	IND Safety Report: Initial & F/U(s)
7/15/2005	323	Response to FDA Clinical Comments for Protocol TMC114-C209
7/18/2005	324	IND Safety Report: Initial
7/20/2005	325	IND Safety Report: Initial & F/U(s)
7/22/2005	326	IND Safety Report: Initial & F/U(s)
7/26/2005	327	IND Safety Report: Initial
7/27/2005	328	IND Safety Report: Initial & F/U(s)
7/28/2005	329	Information Amendment-Clinical
7/29/2005	330	IND Safety Report: Initial & F/U(s)
7/29/2005	331	Protocol Amendment-New Protocol; New Investigator TMC114-C211
7/29/2005	332	Information Amendment- Chemistry, Manufacturing and Controls
8/2/2005	333	IND Safety Report: Initial & F/U(s)
8/3/2005	334	IND Safety Report: Initial & F/U(s)

Date	Serial Number	Submission
8/4/2005	335	IND Safety Report: F/U
8/8/2005	336	Information Amendment – Clinical
8/9/2005	337	IND Safety Report: Initial
8/11/2005	338	IND Safety Report: Initial
8/12/2005	339	IND Safety Report: F/U(s)
8/15/2005	340	IND Safety Report: Initial
8/16/2005	341	Protocol Amendment-New Investigator TMC114-C215
8/17/2005	342	Protocol Amendment-New Investigator TMC114-C214
8/18/2005	343	IND Safety Report: Initial & F/U(s)
8/19/2005	344	Information Amendment-Clinical
8/22/2005	345	IND Safety Report: Initial & F/U(s)
8/23/2005	346	Response to FDA Request for Information
8/24/2005	347	IND Safety Report: Initial & F/U(s)
8/25/2005	348	Information Amendment- Clinical
8/25/2005	349	IND Safety Report: Initial & F/U(s)
8/29/2005	350	IND Safety Report: F/U(s)
8/30/2005	351	IND Safety Report: Initial & F/U(s)
8/31/2005	352	Protocol Amendment-New Investigator TMC114-C202
9/2/2005	353	Information Amendment- Clinical
9/2/2005	354	IND Safety Report: Initial & F/U(s)
9/6/2005	355	IND Safety Report: Initial & F/U(s)
9/7/2005	356	IND Safety Report: Initial & F/U(s)
9/8/2005	357	IND Safety Report: Initial
9/9/2005	358	Information Amendment-Clinical
9/13/2005	359	IND Safety Report: Initial & F/U(s)
9/14/05	360	IND Safety Report: Initial & F/U(s)
9/16/05	361	Information Amendment-Clinical
9/19/05	362	IND Safety Report: Initial & F/U(s)
9/20/05	363	IND Safety Report: F/U(s)
9/21/05	364	IND Safety Report: Initial & F/U(s)
9/22/2005	365	Protocol Amendment-New Investigator TMC114-C214
9/22/2005	366	IND Safety Report: Initial & F/U(s)
9/23/2005	367	Request for Proprietary Name Consultation
9/23/2005	368	IND Safety Report: Initial & F/U(s)
9/23/2005	369	Protocol Amendment-New Investigator TMC114-C209
9/29/2005	370	IND Safety Report: Initial & F/U(s)
10/4/2005	371	IND Safety Report: Initial & F/U(s)
10/5/2005	372	IND Safety Report: F/U(s)
10/5/2005	373	General Correspondence
10/10/2005	374	General Correspondence
10/10/2005	375	Response to FDA Request for Information
10/10/2005	376	IND Safety Report: Initial & F/U(s)
10/12/2005	377	IND Safety Report: Initial & F/U(s)
10/14/2005	378	Information Amendment- Chemistry, Manufacturing and Controls
10/14/2005	379	Request for Consultation
10/17/2005	380	IND Safety Report: F/U(s)
10/17/2005	381	Protocol Amendment-New Investigator TMC114-C202
10/20/2005	382	IND Safety Report: Initial & F/U(s)
10/21/2005	383	7-Day IND Safety Report: F/U(s)
10/24/2005	384	Investigator's Brochure Addendum

Date	Serial Number	Submission
10/24/2005	385	IND Safety Report: F/U(s)
10/26/2005	386	Protocol Amendment-New Investigator TMC114-C215
10/27/2005	387	IND Safety Report: Initial & F/U(s)
10/27/2005	388	Protocol Amendment-New Investigator TMC114-C209
11/1/2005	389	IND Safety Report: Initial
11/7/2005	390	Protocol Amendment - New Investigator TMC114-C214
11/9/2005	391	IND Safety Report: F/U(s)
11/14/2005	392	Protocol Amendment-New Investigator TMC114-C211
11/17/2005	393	Protocol Amendment-New Investigator TMC114-C202
11/18/2005	394	IND Safety Report: F/U(s)
11/23/2005	395	IND Safety Report: Initial
11/28/2005	396	IND Safety Report: Initial
11/29/2005	397	Protocol Amendment-New Investigator TMC114-C215
11/30/2005	398	General Correspondence
11/30/2005	399	Protocol Amendment-New Investigator TMC114-C209
12/1/2005	400	Request for Consultation
12/5/2005	401	IND Safety Report: Initial
12/7/2005	402	Protocol Amendment - New Investigator TMC114-C214
12/8/2005	403	General Correspondence
12/13/2005	404	IND Safety Report: Initial
12/15/2005	405	Protocol Amendment-New Investigator TMC114-C211
12/16/2005	406	IND Safety Report: Initial & F/U(s)
12/19/2005	407	Protocol Amendment-New Investigator TMC114-C202
12/20/2005	408	IND Safety Report: Initial & F/U(s)
12/22/2005	409	Cross Reference Authorization
12/22/2005	410	General Correspondence
12/29/2005	411	Protocol Amendment-New Investigator TMC114-C215
12/29/2005	412	IND Safety Report: Initial
1/4/2006	413	IND Safety Report: Initial & F/U(s)
1/6/2006	414	IND Safety Report: Initial & F/U(s)
1/10/2006	415	Protocol Amendment-New Investigator TMC114-C214
1/12/2006	416	IND Safety Report: Initial & F/U(s)
1/13/2006	417	Response to Request for Information
1/16/2006	418	Protocol Amendment-New Investigator TMC114-C211
1/18/2006	419	IND Safety Report: F/U(s)
1/25/2006	420	IND Safety Report: Initial & F/U(s)
1/26/2006	421	Protocol Amendment-New Investigator TMC114-C202
1/27/2006	422	IND Safety Report: Initial
1/31/2006	423	Protocol Amendment-New investigator TMC114-C215
2/1/2006	424	IND Safety Report: Initial & F/U(s)
2/3/2006	425	Information Amendment- Chemistry, Manufacturing and Controls
2/3/2006	426	Information Amendment-Clinical
2/7/2006	427	IND Safety Report: Initial & F/U(s)
2/7/2006	428	Protocol Amendment-Change in Protocol TMC114-C215,
2/7/2006	429	Protocol Amendment-Change in Protocol TMC114-C202
2/8/2006	430	IND Safety Report: F/U(s)
2/9/2006	431	Protocol Amendment-Change in Protocol TMC114-C209
2/9/2006	432	Protocol Amendment-Change in Protocol TMC114-C214
2/10/2006	433	IND Safety Report: Initial & F/U(s)
2/10/2006	434	Protocol Amendment-New Investigator TMC114-C214

Date	Serial Number	Submission
2/10/2006	435	Protocol Amendment-Change in Protocol TMC114-C211 Response to FDA Comments
2/16/2006	436	IND Safety Report: Initial & F/U(s)
2/21/2006	437	IND Safety Report: Initial & F/U(s)
2/22/2006	438	IND Safety Report: F/U(s)
2/24/2006	439	IND Safety Report: F/U(s)
2/24/2006	440	Protocol Amendment-New Investigator TMC114-C211
2/28/2006	441	IND Safety Report: F/U(s)
3/2/2006	442	IND Safety Report: Initial & F/U(s)
3/3/2006	443	IND Safety Report: Initial & F/U(s)
3/7/2006	444	Response to FDA Comments
3/8/2006	445	IND Safety Report: Initial & F/U(s)
3/9/2006	446	Protocol Amendment-New Investigator TMC114-C209
3/10/2006	447	Protocol Amendment-New Investigator TMC114-C202
3/13/2006	448	Protocol Amendment-New Investigator TMC114-C215
3/14/2006	449	IND Safety Report: F/U(s)
3/15/2006	450	Information Amendment-Clinical
3/20/2006	451	General Correspondence
3/20/2006	452	Investigator's Brochure Edition 7
3/20/2006	453	IND Annual Report
3/20/2006	454	IND Safety Report: Initial
3/21/2006	455	Information Amendment- Chemistry, Manufacturing and Controls
3/22/2006	456	IND Safety Report: F/U(s)
3/23/2006	457	Protocol Amendment-New Investigator TMC114-C214
3/23/2006	458	IND Safety Report: Initial
3/24/2006	459	IND Safety Report: F/U(s)
3/24/2006	460	Protocol Amendment-New Investigator TMC114-C211
3/29/2006	461	IND Safety Report: Initial
3/30/2006	462	IND Safety Report: Initial & F/U(s)
4/5/2006	463	IND Safety Report: Initial
4/7/2006	464	IND Safety Report: Initial & F/U(s)
4/11/2006	465	IND Safety Report: F/U(s)
4/12/2006	466	Protocol Amendment-New Investigator TMC114-C202
4/12/2006	467	Cross Reference Authorization
4/14/2006	468	IND Safety Report: Initial
4/14/2006	469	Protocol Amendment-New Protocol; New Investigator TMC114-C212 Response to FDA Comments
4/14/2006	470	Information Amendment- Chemistry, Manufacturing and Controls
4/19/2006	471	Protocol Amendment-New Investigator TMC114-C215
4/19/2006	472	IND Safety Report: Initial & F/U(s)
4/21/2006	473	Information Amendment – Clinical
4/21/2006	474	IND Safety Report: Initial
4/25/2006	475	IND Safety Report: F/U
4/28/2006	476	Protocol Amendment-New Investigator TMC114-C211
4/28/2006	477	IND Safety Report: F/U(s)
5/1/2006	478	IND Safety Report: Initial & F/U(s)
5/2/2006	479	IND Safety Report: F/U(s)
5/3/2006	480	IND Safety Report: F/U(s)
5/5/2006	481	IND Safety Report: F/U(s)
5/8/2006	482	IND Safety Report: Initial

Date	Serial Number	Submission
5/12/2006	483	IND Safety Report: Initial & F/U
5/15/2006	484	Cross Reference Authorization
5/16/2006	485	Information Amendment – Clinical
5/16/2006	486	IND Safety Report: Initial & F/U(s)
5/17/2006	487	IND Safety Report: Initial
5/19/2006	488	IND Safety Report: Initial
5/19/2006	489	Protocol Amendment-New Investigator TMC114-C202
5/22/2006	490	IND Safety Report: Initial & F/U
5/23/2006	491	IND Safety Report: F/U
5/26/2006	492	IND Safety Report: Initial & F/U(s)
5/30/2006	493	IND Safety Report: Initial & F/U
6/2/2006	494	IND Safety Report: Initial & F/U

NDA 21-976 (PREZISTA; darunavir; TMC114) US eCTD Submission Log

Date	Submission
September 23, 2005	NDA Submission of September Clinical Section
November 4, 2005	NDA Submission of Quality and Non-clinical Sections
November 17, 2005	Response to FDA Request for Information
December 22, 2005	NDA Submission of December Clinical & Non-clinical Sections
February 9, 2006	Amendment to Pending Application
February 27, 2006	Amendment to Pending Application; Response to FDA Request for Information
March 21, 2006	Response to FDA Request for Information
March 29, 2006	NDA Safety Update
April 14, 2006	Response to FDA Request for Information
June 1, 2006	Response to FDA Request for Information; Revised Draft Labeling
June 12, 2006	Response to FDA Request for Information; Revised Draft Labeling
June 19, 2006	Response to FDA Request for Information; Revised Draft Labeling
June 21, 2006	Response to FDA Request for Information; Revised Draft Labeling
June 22, 2006	Revised Draft Labeling; Response to Proposed Postmarketing Commitments
June 29, 2006	Final Printed Labeling for approved NDA 21-976
July 20, 2006	Time Sensitive Patent Information

Abbreviations used in Tables:

F/U Follow-Up

No other patent term has been extended for the same regulatory review period for the approved product, PREZISTA™. 37 C.F.R §1.720(h).

The extension claimed is 717 days, setting the patent to expire on August 12, 2014. The following are the calculations, made in accordance with 37 C.F.R. § 1.775, that result in the claimed extension:

(1) The testing phase began on January 20, 2003 (the effective date of the IND) and ended on December 23, 2005 (submission date of the NDA).

(2) The approval phase began on December 23, 2005 (day of receipt by the FDA of the NDA) and approval was granted on June 23, 2006.

(3) The total number of days in the testing phase (from and including January 20, 2003 to and including December 22, 2005) is 1068 days from the start date to the end date, end date included. One half of the testing phase is 534 days.

(4) The total number of days in the approval phase is (from and including December 23, 2005 to and including June 23, 2006) is 183 days from the start date to the end date, end date included.

(5) The patent issued on June 19, 2001 before the regulatory approval process began.

(6) Applicant acted with due diligence throughout the entire regulatory review period.

(7) The sum of the (a) number of days in one half of the testing phase (534), and (b) number of days in the approval phase (183) is: 717

(8) The original expiration date of the patent is August 25, 2012

(9) Addition of the extension of 717 days to the original expiration date of the patent extends the expiration date of the patent to August 12, 2014.

(10) Fourteen years from the approval date of the product (June 23, 2006) is June 23, 2020.

(11) Pursuant to 35 U.S.C. §156(c)(3), the extended term of the patent cannot exceed 14 years from the date of product approval. The fourteen year cap does not apply since the extension of 717 days sets the patent to expire on August 12, 2014, which is before the date that is 14 years post-approval (June 23, 2020).

(12) Pursuant to 35 U.S.C. §156(g)(6)(A), the extension period is subject to a five year limitation (for patents issued after September 24, 1984). The five year limitation does not apply since the extension of 717 days patent is less than five years.

(13) In light of the conclusions set forth above, the extended expiration date of the '775 Patent is believed to be August 12, 2014.

I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful false statements, and the like so made, are punishable by fine or imprisonment,

Exhibit 8

STATEMENT THAT APPLICANT IS ELIGIBLE FOR EXTENSION AND LENGTH OF EXTENSION CLAIMED

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patent No.: 6,248,775

Issued: June 19, 2001
Expiration Date: August 25, 2012

Inventors: Vazquez; Michael L.; Mueller; Richard A.; Talley; John J.; Getman; Daniel P.; DeCrescenzo; Gary A.; Freskos; John N.; Bertenshaw; Deborah E.; Heintz; Robert M.

Title: α- and ß-Amino Acid Hydroxyethylamino Sulfonamides Useful as Retroviral Protease Inhibitors

Statement of Eligibility for Extension of Patent Term Due to Regulatory Review

I, Alana G. Kriegsman, represent that I am the attorney of record duly appointed by the assignee of the entire right, title and interest in the patent application identified above, and do state on behalf of the Applicant as follows:

To the best of my knowledge, U.S. Patent No. 6,248,775 (the '775 Patent) meets all of the eligibility criteria set forth in 37 C.F.R §§1.710 and 1.720 for extension of patent term.

The '775 Patent claims a "product" as that term is defined in 37 C.F.R §1.710, specifically the active ingredient, darunavir, (present in the form of darunavir ethanolate) of a new human drug, PREZISTA™ 37 C.F.R §1.720(a).

The term of the '775 Patent has never been previously extended. 37 C.F.R §1.720(b).

An application for extension of the term of the '775 Patent in compliance with 37 C.F.R §1.740 is herewith submitted. 37 C.F.R §1.720(c).

The approved product, PREZISTA™, has been subject to a regulatory review period as defined in 35 U.S.C. §156(g). 37 C.F.R §1.720(d).

The approved product, PREZISTA™, has received permission for commercial marketing or use and the permission for the commercial marketing or use of the product is the first received permission for commercial marketing or use under the provision of law under which the applicable regulatory review occurred. 37 C.F.R §1.720(e).

The application for extension of the term of the '775 Patent submitted herewith is submitted within the sixty-day period beginning on the date the product first received permission for commercial marketing or use under the provisions of law under which the applicable regulatory review period occurred. 37 C.F.R §1.720(f).

The term of the '775 Patent, including any interim extension issued pursuant to § 1.790, has not expired before the submission of an application in compliance with 37 C.F.R. § 1.741. 37 C.F.R §1.720(g).

or both, under Section 1001, Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 15 August 2006

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